Copyright

by

Shawn Anthony Kucera

2007

The Dissertation Committee for Shawn Anthony Kucera Certifies that this is the approved version of the following dissertation:

Physical and Chemical Properties of Acrylic Polymers Influencing Physical Aging

Committee:

James W. McGinity, Supervisor

Alan B. Combs

Keith P. Johnston

Christian P. Whitman

Robert O. Williams, III

Physical and Chemical Properties of Acrylic Polymers Influencing Physical Aging

by

Shawn Anthony Kucera, B.A.

Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

December 2007

Dedication

To my family

Acknowledgements

I would like to thank my supervisor, Dr. James W. McGinity, for his kindness and generosity during my studies here at the University of Texas at Austin. Your support and direction have not only helped me in my professional life, but also in my personal life. Thank you for taking this Aggie under your wing and giving him the tools required to become a successful professional.

I would also like to thank the members of my dissertation committee: Dr. Alan B. Combs, Dr. Keith P. Johnston, Dr. Christian P. Whitman, and Dr. Robert O. Williams III. Your time, advice, and encouragement are much appreciated.

My appreciation is extended to Dr. Navnit Shah, Dr. A. Waseem Malick, and Dr. Martin H. Infeld of Hoffmann-LaRoche in Nutley, NJ for their continued support of my research.

Many thanks to the faculty and staff of the UT College of Pharmacy: Dr. James W. McGinity, Dr. Robert O. Williams III, Dr. Jason T. McConville, Dr. Robert Pearlman, Dr. Saloman Stavchansky, Ms. Yolanda Abasta-Ruiz, Mr. David Fudell, Mr. Jay Hamman, and Ms. Belinda Gonzalez-Lemkuhle. Many thanks to Ms. Mickie Sheppard for her patience and untiring assistance in helping me obtain teaching and research assistantships, as well as her direction in the application for scholarships and fellowships. Special thanks to Ms. Claudia McClelland, my "lab mom". Your excellent record-

keeping and managerial skills always made sure that I was up-to-date on my various memberships. You are truly Dr. McGinity's "right-hand woman".

I wish to thank my family: Mom, Dad, and Leslie. Thank you for your love, support, encouragement, and advice. Without you, I would most definitely not be here today.

Many thanks to my favorite cycling partner, and girlfriend, Ms. Sandra Schilling. You are truly one of the brightest and most caring people I know. Thank you for your understanding of my "strange American ways" and your love and support.

I would also like to thank my friends and colleagues from the University of Texas College of Pharmacy: Dr. Michael Crowley, Dr. Weijia Zheng, Dr. Chris Young, Dr. Jason Vaughn, Dr. Kirk Overhoff, Dr. Dave Miller, Alan Watts, Jim Dinunzio, Mamoru Fukuda, Hiroto Bando, Caroline Bruce, Dorothea Sauer, Dr. Prapasri Sinswat, Dr. Jiahui Hu, Dr. Tom Leach, Dr. Troy Purvis, Wei Yang, Justin Tolman, Tarik Khan, Michael Boquet, and Loni Coots. My appreciation is also extended to my friends and colleagues during my internship at Degussa Pharma Polymers in Darmstadt, Germany: Mr. Manfred Aßmus, Dr. Brigitte Skalsky, Dr. Thomas Fuerst, Diego Gallardo, Kathrin Nollenberger, Toshi Tsutsumi, Silke Goelz, Melanie Siefert, and Odette Hensel; as well as the many friends that made for a very exciting summer internship: Kevin Kiehm, Ulrike, Agnes, Martin Kuntsmann, Markus Etz, Sebastian Roth, Thomas Weber, Florian, Juergen, and Thomas. A special thanks to my two interns, Doreen Stimpel and Claudia Tessmann. Your help with my research is greatly appreciated.

Physical and Chemical Properties of Acrylic Polymers Influencing Physical Aging

Publication No._____

Shawn Anthony Kucera, Ph.D.

The University of Texas at Austin, 2007

Supervisor: James W. McGinity

The influence of water soluble and insoluble stabilizing excipients on the physical stability of coated dosage forms was investigated in this study. The effect of the excipients on the thermal and physico-mechanical properties, and water vapor permeability of free films was studied, as was the influence of these excipients on the physical stability and release kinetics of coated pellets.

The effect of water-soluble proteins, bovine serum albumin (BSA) and Type B gelatin, on the physical aging of Eudragit® RS/RL 30 D films was investigated. It was found that ionic interactions occurred above the isoelectric point of BSA and caused unstable films which showed accelerated decreases in drug release rate. The adjustment of the pH of the dispersion below the isoelectric point of BSA resulted in electrostatic repulsive charges that stabilized the drug release rate from coated dosage forms at both ambient and accelerated conditions. The addition of gelatin to the coating dispersion increased the drug release rate due to the formation of gel-domains through which the drug was able to easily diffuse. The influence of silicon dioxide on the stability of

Eudragit® RS/RL 30 D films was investigated. Colloidal grades showed enhanced incorporation in the acrylic matrix; however, unstable films were formed. The addition of silicon dioxide with a larger particle size increased the permeability of the film and stabilization in drug release rate was attributed to constant water vapor permeability values of free films. The influence of ethylcellulose on the physical aging of Eudragit® NE 30 D coated pellets was studied. The two polymers were found to be substantially immiscible and the drug release rate of coated pellets was constant at both ambient and accelerated conditions which correlated to stabilizations in both the physico-mechanical properties and water vapor permeability of free films. Blending both Eudragit® NE 30 D and RS 30 D resulted in the formation of coherent films without the need of plasticizer. The two polymers were found to be miscible and both films and coated dosage forms were stable when stored below the glass transition temperature of the polymer blend. When films were stored above this temperature, instabilities occurred as a result of the further coalescence and densification of the polymer blend.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction – Physical Aging of Polymers and Its Effect on the Stability of Solid Oral Dosage Forms[1]

1.1 Film Formation from Aqueous Latex and Pseudolatex Dispersions

Film-coating is an effective method to modify drug release from tablets and pellets. Aqueous-based coating technology is becoming more popular due to the stringent requirements by environmental and regulatory bodies which restrict the use of organic solvents in production. The formation of thin, transparent films from aqueous-based latex or pseudolatex dispersions occurs with the simultaneous evaporation of water [1, 2] in three stages. During the coating process (stage 1), water evaporates from the film-coated substrate at a constant rate. The latex particles begin to pack together and fuse to form a continuous film. As the colloidal particles begin to fuse and coalesce, stage 2, the rate of water evaporation decreases. By stage 3, film formation is considered complete; however, it is during stage 3 that changes occur in the drug release rate due to physical aging of the polymeric film coating.

1.2 A History of Physical Aging

Physical aging, or enthalpy relaxation, has been known to polymer scientists for many years. All amorphous polymers show physical aging, where the material becomes more rigid, brittle, and dense with time [3]. In the text titled "Physical Aging in Amorphous Polymers and Other Materials" [4], Struik discussed the early work of Simon [5] who had shown that amorphous materials were not in thermodynamic equilibrium at temperatures below their glass transition temperature. The dynamic state is a result of the materials possessing a volume, enthalpy, and entropy that are greater than in the equilibrium state. The free volume concept states that transport mobility of particles in a

[1] Published in part by: Kucera, S.A., et al. (In Press, 2008) 'Chapter 15: Physical Aging of Polymers and Its Effect on the Stability of Solid Oral Dosage Forms' in McGinity, J.W. & Felton, L.A. (eds.) *Aqueous polymeric coatings for pharmaceutical dosage forms, 3rd edn*. New York: Informa Healthcare, USA. pp. 447-476.

closely packed system primarily depends on the degree of packing, or the free volume. When the polymer is cooled to some temperature below it glass transition temperature (Tg), the mobility will be small, but not zero. At this stage, the free volume is greater than it would be at equilibrium and the volume will decrease slowly [4, 6]. This contraction is accompanied by a decrease in the polymer chain mobility, which leads to a densification of the polymer, influencing both porosity and tortuosity [6, 7].

1.3 THE EFFECT OF PHYISCAL AGING ON DIFFUSIONAL DRUG RELEASE

Diffusion of a drug molecule through a thin film is governed by Fick's First Law of Diffusion:

$$Q = \frac{D \times S \times (C_1 - C_2) \times t}{h} \qquad \text{(Eq. 1.1)}$$

where Q (the amount of drug diffused over a period of time, t) is a function of h, the film thickness; S, the surface area available for diffusion; C_1, the concentration of drug in the donor compartment; C_2, the concentration of drug in the acceptor compartment, and D, the diffusion coefficient of the drug. The physical aging of a polymeric film results in a change in the diffusion coefficient [7, 8], which can be shown by the Iyer Equation (equation 1.2):

$$D = \frac{D_w \times e}{\tau} \qquad \text{(Eq. 1.2)}$$

where D_w is the diffusion coefficient of the drug in water. D is the diffusion coefficient of the drug and is a function of both the film's porosity, e, and tortuosity, τ. As a film ages, it becomes more dense [3], resulting in a decrease in film porosity and an increase in tortuosity, thus causing a decrease in the dissolution rate of drug from film-coated dosage forms over time [7].

1.4 METHODS OF QUANTIFYING PHYSICAL AGING

The physical changes in pharmaceutical polymers resulting from aging can be evaluated and quantified by a number of analytical methods, including measurement of the Tg, typically done by differential scanning calorimetry (DSC), analysis of mechanical properties or film permeability, dissolution of drug from a coated dosage form, and by free volume measurements. The presence of drug crystals on the surface of the coating, which can also indicate polymer aging, can be studied using powder x-ray diffraction (PXRD) and scanning electron microscopy (SEM).

1.4.1 Mechanical Analysis

When a polymer is cooled below its glass transition temperature, the amorphous material has a higher specific volume, enthalpy, and entropy than the equilibrium state would possess at the same temperature [9]. The structural changes in the glassy state due to relaxation of the polymer can manifest changes in the physical properties that are of critical importance to pharmaceutical scientists. These changes include decreases in elongation [7, 9, 10] and creep compliance [11] as well as increases in elastic modulus [9, 10] and tensile stress [7, 10]. These parameters are all quantifiable by examining the physical-mechanical properties of polymeric films as a function of time and storage conditions.

1.4.1.1 Unilateral Stress-Strain

A simple method to examine the physical-mechanical properties of polymeric films is by unilateral stress-strain experiments [6, 7, 10-18]. Changes in the internal structures of polymers strongly affect their physical and mechanical properties [19] and the results from stress-strain experiments allow the researcher to gather information on the tensile properties, modulus, and elongation of thin films [7]. The industry standard for these measurements is published by the American Society for Testing Materials (ASTM) D 882-02: Standard Test Method for Tensile Properties of Thin Plastic Sheeting

[20]. The specimen to be tested should have a thickness of less than 1.0 mm, a width between 5.0 and 25.4 mm, and should be at least 50 mm longer than the grip separation. If possible, the specimens used for the test should have an overall thickness that is uniform within 10%.

To begin testing, the film specimen is placed in the grips of an instrument such as an Instron testing device. One grip of the device is fixed, while the other is allowed to move at a constant rate. As the movable grip is extended, the film is subjected to strain, which is recorded by the instrument with either a tracer/plotter attachment or, as seen in newer equipment, a computer having specialized software packages. These software packages, such as Bluehill distributed by Instron, allow for the automatic calculation of such parameters as tensile strength at break or maximum load, percent elongation, and the elastic or Young's modulus of a film specimen.

1.4.1.2 Creep Compliance

Creep testing is another common method that allows scientists to measure the changes in physical-mechanical properties of a polymer as it ages [6, 11, 14, 17, 21-27]. Creep is the progressive deformation of a material at a constant load. Creep tests measure the dimensional changes that occur over time under a constant static load that is applied to the specimen at a set temperature [28].

The creep of a specimen occurs in 3 stages. Following an initial rapid elongation upon application of the load, the creep rate decreases rapidly with time during Stage 1. Stage 2 is denoted by the attainment of a steady state with respect to creep rate. Stage 3 is characterized by a rapid increase in creep rate followed by fracture of the specimen. Graphically, when plotted as a log-log plot, the creep compliance of a material is linear in relation to time [28]. During physical aging, creep compliance decreases as indicated by an increase in the slope of creep modulus versus time on a log-log plot.

The industry standard for creep testing is ASTM D 2990-01: Standard Test Methods for Tensile, Compressive, and Flexural and Creep-Rupture of Plastics [28].

Specimens for tensile creep measurements should conform to the same standards as those used in unilateral stress-strain experiments. For this experiment, the film sample is first placed between two clamps and then annealed by raising the temperature about 10-20°C higher than the polymer's Tg and cooled or quenched to some pre-defined temperature below the Tg of the polymer for a period of time, usually a few minutes.

1.4.2 Membrane Permeability

Measuring the vapor permeability of a film as a function of time and aging conditions has been previously used to qualitatively analyze physical aging in thin polymeric films [7, 11, 13, 15, 24, 29-37]. As the film undergoes further gradual coalescence, its permeability to a gas will decrease due to increases in film density and tortuosity. As physical aging progresses, a decrease in water vapor transmission rate is typically observed.

1.4.2.1 Water Vapor Permeability

The water vapor transmission rate is the steady flow of water vapor per unit time through a unit area under specific conditions of temperature and humidity [38]. A useful guideline is published by the American Society for Testing Materials (ASTM) E 96/E 96 M-05. The guideline describes two methods for determining the moisture vapor permeability of a thin film. One method, known as the desiccant method, involves placing a thin polymer film over the opening of a cup containing anhydrous calcium chloride as a desiccant. The film is secured and the apparatus is placed in a constant-temperature, constant-humidity environment. The cup is weighed periodically and a graph of weight vs. time is plotted. The second method is called the water method and the cup contains a saturated salt solution of known relative humidity rather than a desiccant. With this method, the permeability of the film is evaluated by quantifying the transfer of water vapor from the cup through the specimen to a controlled atmosphere over time.

The rate of water vapor transmission can be calculated using equation 1.3:

$$WVT = \frac{G}{tA} \qquad \text{(Eq. 1.3)}$$

where WVT is the water vapor transmission in g/h·m2, (G/t) is the slope of the line from the weight gain vs. time plot, and A is the surface area of the film. These data can be used to calculate the permeability of a thin film. Permeability is simply the arithmetic product of permeance and thickness, where permeance is the rate of water vapor transmission through the film as a function of vapor pressure differences between the two surfaces. Permeance is a performance measure of the film, whereas permeability is a property of the material. The permeance of the film can be calculated using equation 1.4:

$$Permeance = \frac{WVT}{\Delta p} = \frac{WVT}{S(R_1 - R_2)} \qquad \text{(Eq. 1.4)}$$

where S is the saturation vapor pressure at test temperature, R_1 is the relative humidity at the source (in the chamber for the desiccant method and in the cup for the water method), and R_2 is the relative humidity at the vapor sink. The permeability of the film is calculated by multiplying the thickness of the film by its permeance.

1.4.3 Free Volume Measurements

1.4.3.1 Ellipsometry

Ellipsometry is an optical technique for measuring the dielectric properties (i.e., refractive index) of thin films [34-36, 39-41]. Huang and Paul first reported on the use of ellipsometry in monitoring the physical aging of thin glassy films by changes in refractive index [39]. This method has the advantage that no damage is done to the film specimen, allowing the same sample to be examined throughout an aging study.

The Lorentz-Lorenz parameter (L) is derived from the Lorentz-Lorenz equation (equation 1.5) [39]:

$$L = \frac{n^2 - 1}{n^2 + 2} = \frac{\rho N_{av} \alpha}{3 M_0 \varepsilon_0} \qquad \text{(Eq. 1.5)}$$

and shows that the refractive index (n) is directly related to ρ, the density of the polymer, where N_{av} is Avogadro's number, α is the average polarizability of the polymer repeat unit, M_0 is the molecular weight of the polymer repeat unit, and ε_0 is the permittivity of free space constant.

The Lorentz-Lorenz parameter (equation 1.5) can also be related to the density of a polymer by equation 1.6 [41]:

$$L = \rho C \qquad \text{(Eq. 1.6)}$$

where ρ is the density of the material and C is a material constant from the bulk values of refractive index and density at 25°C [41]. The fractional free volume, f, at any time is then determined by equation 1.7 [41]:

$$f = \frac{V - V_0}{V} = 1 - \rho V_0 = 1 - \frac{L}{C} V_0 \qquad \text{(Eq. 1.7)}$$

where $V=1/\rho$ is the specific volume at that aging time, V_0 is the occupied volume of the polymer computed from the van der Waals volume of the polymer, V_w, by the Bondi method, where $V_0=1.3V_w$ [41].

1.4.3.2 Positron Annihilation Spectoscopy (PALS)

Another method used to quantify the changes in free volume due to the physical aging of polymeric films is by the use of positron annihilation spectroscopy (PALS) [17, 42-45]. This method is able to measure the free volume as well as the free volume distribution in a polymeric film [17, 44, 46]. The positron is a particle that has the same

properties of an electron, however, with an opposite charge. When a positron and an electron meet, it is likely that a positronium atom will form [46]. There are two possibile positronium "states" that can exist: the para-positronium (p-Ps) and the ortho-positronium (o-Ps). While the p-Ps state has a very short life of about 125 ps [46] in a vacuum, the o-Ps has a relatively long lifetime of about 142 ns [46] under the same conditions and a lifetime of about 1-10 ns in a polymer [44]. When the o-Ps atom annihilates, three gamma rays are emitted and detected to determine the lifetime of the particle.

In a PALS experiment, a radioactive sample of ^{22}NaCl [22, 44, 46] is used to inject lone positrons into the polymer sample. The lifetime of the positron in the sample (λ) is therefore due to the electron density at the location of the positron according to equation 1.8 [44]:

$$\lambda = C\int \rho_+ \rho_- dV \quad \text{(Eq. 1.8)}$$

where C is a constant and ρ_+ and ρ_- are the positron and electron densities, respectively. The lifetime of the o-Ps particle (in nanoseconds), τ, is described by equation 1.9 [44-46]:

$$\tau = \frac{1}{2}\left[1 - \frac{R}{R+\Delta R} + \frac{1}{2\pi}\sin\left(\frac{2\pi R}{R+\Delta R}\right)\right]^{-1} \quad \text{(Eq. 1.9)}$$

where R is the radius of the spherical free volume holes and ΔR represents the thickness of the electron layer which is a constant of 1.656Å [22, 46]. Thus, there is a direct correlation between the lifetime of the o-Ps and the size of the free volume voids in the polymer matrix [22].

1.4.4 Thermal and Microscopic Analysis

Differential scanning calorimetry (DSC) is a common analytical method used to determine various polymer properties, including melting temperature, degree of

crystallinity, Tg, and enthalpy of transition. The technique is widely used to investigate excipient-polymer interactions and evaluate the effectiveness of plasticizing agents in polymeric films. A film sample and a reference are heated at a programmed rate and more energy is absorbed (or emitted) in the sample during a phase change. The energy or heat flow is plotted against temperature or time and software programs are used to determine the desired property. During physical aging, there is a decrease in enthalpy or enthalpy of relaxation and can be measured by DSC. This parameter is commonly used to study physical aging and can be determined by integrating the endothermal peak present in the Tg region during the initial scan [47]. As the polymer ages, both the peak size and the temperature corresponding to its maximum will increase [17, 47].

Polymer films may contain various additives such as endogenous emulsifiers, active pharmaceutical ingredients, or excipients that either improve processability or modify drug release from the coated dosage forms. In some cases, the polymer may be stored at a temperature above the Tg. At this point, the specific volume of the polymer is large as is the molecular mobility of the polymer and it is possible for the additive components to crystallize during storage. Techniques such as DSC, PXRD, and SEM can be used to scan the polymeric films to determine if crystal growth is present.

1.5 VARIABLES THAT INFLUENCE PHYSICAL AGING

1.5.1 Plasticizers

Plasticizers reduce the intermolecular attractions between polymer chains to increase the flexibility of the resulting film and enhance the formation of thin films from aqueous lattices. The selection of a plasticizer is of the utmost importance when formulating a coating dispersion. Plasticizers must remain in the film, exhibiting little or no tendency for migration or volatilization. Moreover, plasticizers must be compatible with the polymer. Using a plasticizer that is incompatible with an aqueous latex can result

in poor film formation and instabilities with respect to drug release over time during storage.

Once incorporated, the plasticizing agent should remain in the polymeric matrix in order to produce a stable film. The permeability and mechanical strength of Eudragit® RS and RL films were found to be a function of plasticizer remaining in the film [30]. Both films exhibited a decrease in plasticizer content after 6 months of storage at 25°C/0% RH and a concomitant decrease in the elongation at break. In contrast, the permeability of RS films decreased during this time period, while the RL films demonstrated an increase in permeability. These results were attributed to the volatilization of the plasticizer. The loss of plasticizer was less critical for the more hydrophilic RL polymer, with the void space being quickly filled by the permeant solution, thus resulting in an increase in permeation.

The addition of a proper amount of plasticizer to the coating dispersion is also of considerable importance. Incorporation of an inadequate amount of plasticizer in the formulation can result in polymer films that are brittle or that require longer curing times to exhibit stable films. The degree of coalescence of latex particles at the end of the coating process is a function of the concentration of plasticizer in the formulation, with higher concentrations of plasticizer producing enhanced or more complete film formation. In one study, theophylline release from pellets coated with Eudragit® RS 30 D containing 5% Pharmacoat 606 and 10 or 20% TEC as a plasticizer was investigated [48]. The time to achieve a stable drug release rate at storage conditions of 40°C and 50% relative humidity ranged between 6 months and 10 days for formulations containing 10% and 20% plasticizer, respectively.

1.5.2 Curing and Storage Conditions

After completion of the coating process, coated dosage forms are often stored at elevated temperatures to promote further gradual coalescence of the film, a process known as curing. Curing of film-coated dosage forms is an important component in the

film-formation mechanism of thin films from aqueous lattices. The film formation process from these aqueous dispersions relies on capillary forces to draw together and deform the latex particles and is influenced by the amount of water in the polymeric film. As the amount of water in the polymer film increases, the Tg of the film is lowered, resulting in an increased mobility of the polymer chains which in turn enhances the further coalescence of the latex particles. As the humidity of the environment is decreased, the amount of water in the polymeric film is reduced and consequently the capillary forces that facilitate film formation are not present.

Although the presence of water can help to enhance the coalescence of polymeric films during curing, high levels of humidity during storage can destabilize the films, leading to changes in the drug release rate over time. Water will function as a plasticizer in film-coated dosage forms and enhance coalescence of polymeric films during storage, which will generally result in a decrease in the drug release rate.

Both curing temperature and curing time significantly affect the drug release rate, but curing temperature is of greater consequence [49-51]. Lin and coworkers [50] showed a decrease in the dissolution rate of diphenhydramine from pellets coated with a 10% weight gain of Eudragit® NE 30 D at curing temperatures of 30°C, 45°C, and 60°C. The decrease in release rate of the product stored at 30°C was small (when compared to other temperatures) and not significantly affected by length of curing time. However, as temperature and storage time were increased, the changes observed in the dissolution rate were amplified. It is suggested that in order for the polymer to achieve a stable energetic state, energy is required to overcome existing barriers that cause the stable state to be kinetically disfavored. At higher temperatures, more polymer molecules can overcome this energy barrier and reach the stable state, which is reflected by a slower drug release rate. On the other hand, at lower curing temperatures, fewer molecules can achieve the stable state, meaning that changes in drug release would be expected to occur slowly over time until this stable state is reached.

Changes in drug release during curing have also been reported for high glass transition temperature polymers, such as ethylcellulose, in dosage forms coated with Aquacoat® ECD. Physical instabilities in the coating can cause cracking and chipping of the film coating; however, researchers attributed these problems to an increase in the water content of the films rather than a decrease [31]. Incomplete film formation and further gradual coalescence during storage of dosage forms coated with Aquacoat® will cause instability in the drug release rate. Contrary to the stability problems seen in acrylic polymers, uncured Aquacoat® ECD films actually exhibited an increase in drug dissolution rate, rather than a decrease. Faster drug release may be caused by brittle films or the formation of microruptures in the film coat during storage [52]. For films cast from an organic solution, there is a significant shift in creep compliance as aging progresses, indicating a decrease in free volume of the film and increased compaction of the polymer structure. These changes were also responsible for a reduction in the water vapor permeability coefficient as a function of aging time [11]. For aqueous-based films, a decrease in free volume was noted as a result of further gradual coalescence of the pseudolatex particles [13].

1.5.3 Endogenous Excipients

The presence of endogenous excipients in aqueous coating systems is often necessary to stabilize the dispersion during storage. In other cases, excipients are used in the emulsion polymerization process of aqueous lattices, as is the case of nonoxynol 100 in Eudragit® NE 30 D dispersions. However, the presence of this emulsifier can lead to serious stability issues, such as an increase in drug dissolution rate during storage [53]. Due to the relatively high melting point of the surfactant (~60°C), it is possible for the material to crystallize within the film during storage at room temperature. Studies have shown that crystallization of the surfactant affects the dissolution rate of drug from coated dosage forms [54]. Further gradual coalescence and drug release from coated pellets were influenced by increasing amounts of nonoxynol 100 in the coating

dispersions [54]. When a commercially available Eudragit® NE 30 D dispersion (1.5% nonoxynol 100) was used to coat pellets, the drug release rate diminished by 10% over two months storage at room temperature, while a decrease of only 5% was observed when the nonoxynol 100 concentration was 5%. However, when the surfactant concentration was increased to 10%, there was first a decrease in the dissolution rate of the drug as a result of the initial swelling of the polymer, after which the dissolution rate of the drug increased. This phenomenon was the result of further coalescence of the polymer, which decreased the drug release rate, coupled with the dissolution of surfactant crystals, which caused large pores in the film and enhanced the release of the drug [54].

The crystallization of nonoxynol 100 in Eudragit® NE 30 D free films has also been followed via calorimetric studies [55]. These studies showed the melting point of nonoxynol 100 as a single endothermic peak at around 55°C for freshly cast films of Eudragit® NE 30 D. The films were stored at ambient conditions (25°C/<35% RH), 25°C/60% RH, and 40°C/75% RH and analyzed via DSC at periods of 1, 2, and 4 weeks. As time progressed, all films showed an increase in the magnitude of the melting point endotherm of nonoxynol 100, indicating crystal growth of the surfactant in the film, which agrees with earlier data published by Lin and Augsburger [54]. The study also concluded that lower temperatures caused a higher degree of crystallization of the emulsifying agent.

Positron annihilation lifetime spectroscopy was used to measure the distribution of free volume holes in cast films of Eudragit® NE 30 D with and without nonoxynol 100 [44]. When the emulsifying agent was not present in the film, the size distribution of free volume holes remained unchanged when stored for 30 days at 25°C/75% RH. When nonoxynol 100 was present in the film however, the size distribution of the free volume holes narrowed and was more uniform following initial sample preparation. During one month's storage at conditions of high humidity, water initiated an absorption-dissolution transition in these films and the size distribution of the free volume holes in the polymer

increased. This report confirms earlier studies [50, 54, 55] that indicated nonoxynol 100 affects the long-term stability of Eudragit® NE 30 D films.

1.6 METHODS USED TO STABILIZE/PREVENT AGING

1.6.1 Increased Plasticizer Concentration

Plasticizers lower both the glass transition temperature and the minimum film formation temperature of the polymer. Furthermore, the degree of coalescence of latex particles at the completion of the coating process increases as the amount of plasticizer in the formulation increases due to the plasticizer's ability to weaken polymeric intermolecular attractions thus allowing the polymer molecules to move more readily, increasing the flexibility of the polymer. For example, theophylline pellets coated with a formulation containing Eudragit® RS 30 D, 5% Pharmacoat 606, 50% talc, and 30% TEC showed virtually no change in dissolution rate upon storage [48].

While liquid plasticizers can be lost through evaporation during storage, solid-state plasticizers have the distinct advantage of remaining in the film through the life of the dosage form. Studies have been conducted in which non-pareil beads were coated with Eudragit® RS 30 D containing 40% ibuprofen as the active ingredient and solid-state plasticizer [56]. The coated beads were cured at 40°C for a period of 24 hours and then stored at 23°C and 0% relative humidity. No significant difference was found between the initial drug release rate and the drug release profiles of the stored samples. The authors reported that the presence of ibuprofen in the coating also served as an anti-adherent, preventing the agglomeration of pellets during the coating process and subsequent storage.

1.6.2 Curing and Storage

The conditions at which dosage forms are cured, as well as stored, can have a significant effect on the stability of the polymeric film. When dosage forms are cured at high temperatures, the time required to reach a fully coalesced film decreases in

comparison to curing at lower temperatures [52]. At temperatures above the Tg of the film, the mobility of the polymer chains increases and latex coalescence is accelerated so that films are nearly completely coalesced when removed from the coating apparatus.

Humidity in the environment during storage can significantly influence drug release from coated dosage forms. Water vapor in the atmosphere which is adsorbed by the polymeric films can act as a plasticizer, increasing the molecular mobility of the polymer and aiding in the densification and further coalescence of the polymer. In the case of acrylic films cast from organic solutions [11], the time required for a fully coalesced film to form was shown to be longer than the same film cast from an aqueous system. Curing of these films at low humidity conditions under vacuum was not effective for removing the solvent from the films; however, higher humidity conditions were found to facilitate solvent removal.

1.6.3 Addition of High Glass Transition Temperature Polymers

The addition of a miscible, high glass transition polymer is another method which has been shown to stabilize drug release from sustained release coatings. Stabilization occurs by decreasing molecular mobility of the polymer film by increasing the Tg of the polymer blend. High glass transition temperature polymers also serve as a framework to resist the densification and further coalescence of a continuous phase with a much lower glass transition temperature. As an example, Eudragit® L 100-55 was found to be miscible with Eudragit® RS 30 D [57], and although the enteric polymer increased the drug release rate from coated theophylline pellets as the pH of the dissolution media increased, the product exhibited no physical aging when stored at 40°C, i.e. a static drug release profile over time. Another study [58] showed that the addition of 16.7% Eudragit® L 30 D-55 to Eudragit® NE 30 D decreased the tackiness of the films and, when cured at 60°C, the drug release rate of the coated pellets stabilized after 4 hours of storage.

1.6.4 High Solids Content

Talc is traditionally used as an anti-tacking agent in the coating formulation and is usually present at concentrations of 50-100%. Generally, the addition of higher amounts of talc is seldom used because the high solids content could alter drug release from the dosage form. However, it has been shown that the inclusion of up to 200% talc can be used to successfully formulate coated pellets with a sustained drug release rate [59]. When this amount of talc was added to a 95:5 blend of Eudragit® RS/RL 30 D plasticized with TEC, the acrylic polymer functioned as an effective binder for the talc, resulting in a continuous film coat. However, although film formation was incomplete, the coating still provided a sustained release of the drug. The high talc content of the films also resulted in no agglomeration of the coated pellets during curing at 60°C or storage at 40°C/75% RH in open containers. The authors stated that the addition of 10 or 20% TEC to the coating formulation resulted in dosage forms which were physically stable and no significant change in drug release rate was noticed during storage for 3 months.

1.6.5 Addition of Immiscible, Hydrophilic Excipients

Hydrophilic, water soluble polymers have found use in stabilizing sustained release polymers in coating applications. It has been shown that these excipients form boundaries which inhibit the further coalescence of the functional polymer. For example, hydroxyethylcellulose (HEC) has been shown to stabilize the release rate of theophylline from pellets coated with Eudragit® RS 30 D [7]. Theophylline pellets coated with the acrylic polymer plasticized with 20% TEC exhibited a decrease in drug release rate during storage at 25°C/60% RH. Cast films of the same formulation showed an increase in tensile strength and a decrease in water vapor transmission rate during storage over 1 month. The addition of 10% HEC to the coating formulation, however, stabilized the drug release profiles of the coated pellets stored at the same conditions. Likewise, no changes were observed in the physical-mechanical properties or the water vapor transmission rate of the cast films containing HEC. Atomic force microscopy (AFM)

was used to characterize the surface morphology of the cast films. Films of Eudragit® RS 30 D exhibited a smooth, regular surface where all latex particle boundaries had disappeared. In contrast, a rough surface was observed for acrylic films containing 10% HEC. The hydrophilic polymer had surrounded the hydrophobic acrylic latex particles and prevented the further coalescence and densification of the film. The HEC allowed the film structure to be retained during storage and stabilized the permeability and mechanical properties of the film.

1.7 CONCLUSIONS

Physical aging is a phenomenon that affects all polymers. Simply utilizing alternative coating systems or polymers is not the solution to formulations that exhibit these stability issues. The subject has been extensively discussed in the chemical engineering literature and is an important consideration during formulation development for pharmaceutical scientists. Physical aging of polymers has been shown to cause changes in the physical-mechanical, permeability, and drug release properties of polymeric films due to a densification and decrease in free volume of the polymer as it relaxes to an equilibrated thermodynamic state. Since the coating of oral dosage forms with aqueous polymeric lattices is one of the simplest and most widely used methods for controlling drug release rates, the stability of these coated dosage forms is of the utmost importance. Aging has been shown to be influenced by factors such as humidity and temperature during storage as well as excipients in the coating formulation. A number of techniques have been used to stabilize polymeric films and prevent aging. Care must be taken to both plan for and identify potential aging issues during the early stages of product development. This includes determining the mechanism or mechanisms of destabilization, identifying the most appropriate stabilizer for the coating formulation, and ensuring that the coated dosage forms are cured to a point that film formation from the aqueous latex is complete.

1.8 REFERENCES

1. Lin, F. and D.J. Meier. A Study of Latex Film Formation by Atomic Force Microscopy. 1. A Comparison of Wet and Dry Conditions. Langmuir, 1995. **11** (7): p. 2726-2733.

2. Lippold, B.C. and R.M. Pages. Film Formation, Reproducibility of Production and Curing with Respect to Release Stability of Functional Coatings from Aqueous Polymer Dispersions. Pharmazie, 2001. **56** (1): p. 5-17.

3. Greiner, R. and F.R. Schwarzl. Volume relaxation and physical aging of amorphous polymers I. Theory of volume relaxation after single temperature jumps. Colloid & Polymer Science, 1989. **267** (1): p. 39-47.

4. Struik, L.C.E. *Chapter 1 - Scope of the Work*, in *Physical Aging in Amorphous Polymers and Other Materials*, L.C.E. Struik, Editor. 1978, Elsevier Scientific Publishing Company: New York. p. 1.

5. Simon, F. Z. anorg. allgem. Chem., 1931. **23** p. 219.

6. Guo, J.-H. Aging processes in pharmaceutical polymers. Pharm. Sci. Technol. Today, 1999. **2** (12): p. 478-483.

7. Zheng, W., D. Sauer, and J.W. McGinity. Influence of hydroxyethylcellulose on the drug release properties of theophylline pellets coated with Eudragit® RS 30 D. European Journal of Pharmaceutics and Biopharmaceutics, 2005. **59** (1): p. 147-154.

8. Iyer, U., W.-H. Hong, N. Das, and I. Ghebre-Sellaissie. Comparative evaluation of three organic solvent and dispersion-based ethylcellulose coating formulations. Pharm. Tech., 1990. **14** (9): p. 68-86.

9. Priestley, R.D., C.J. Ellison, L.J. Broadbelt, and J.M. Torkelson. Structural Relaxation of Polymer Glasses at Surfaces, Interfaces, and In Between. Science, 2005. **309** (5733): p. 456-459.

10. Gutierrez-Rocca, J.C. and J.W. McGinity. Influence of Physical Aging on the Physical-Mechanical Properties of Acrylic Resin Films Cast from Aqueous Dispersions and Organic Solutions. Drug Dev. Ind. Pharm., 1993. **19** (3): p. 315-332.

11. Guo, J.-H., R.E. Robertson, and G.L. Amidon. Influence of Physical Aging on Mechanical Properties of Polymer Free Films: The Prediction of Long-Term Aging Effects on the Water Permeability and Dissolution Rate of Polymer Film-Coated Tablets. Pharmaceutical Research, 1991. **8** (12): p. 1500-1504.

12. Sinko, C.M., A.F. Yee, and G.L. Amidon. Prediction of Physical Aging in Controlled-Release Coatings: The Application of the Relaxation Coupling Model to Glassy Cellulose Acetate. Pharmaceutical Research, 1991. **8** (6): p. 698-705.

13. Guo, J.-H., R.E. Robertson, and G.L. Amidon. An Investigation into the Mechanical and Transport Properties of Aqueous Latex Films: A New Hypothesis for the Film-Forming Mechanism of Aqueous Dispersion System. Pharmaceutical Research, 1993. **10** (3): p. 405-410.

14. Matsumoto, D.S. Time-temperature superposition and physical aging in amorphous polymers. Polymer Engineering & Science, 1988. **28** (20): p. 1313-1317.

15. Heng, P.W.S., L.W. Chan, and K.T. Ong. Influence of Storage Conditions and Type of Plasticizers on Ethylcellulose and Acrylate Films Formed from Aqueous Dispersions. J Pharm Pharmaceut Sci, 2003. **6** (3): p. 334-344.

16. Omari, D.M., A. Sallam, A. Abd-Elbary, and M. El-Samaligy. Lactic acid-induced modifications in films of Eudragit® RL and RS aqueous dispersions. International Journal of Pharmaceutics, 2004. **274** (1-2): p. 85-96.

17. Hutchinson, J.M. Physical aging of polymers. Progress in Polymer Science, 1995. **20** (4): p. 703-760.

18. Dai, C.-A. and M.-W. Liu. The effect of crystallinity and aging enthalpy on the mechanical properties of gelatin films. Materials Science and Engineering: A Mechanical Behaviour of Micro- and Nano-scale Systems, 2006. **423** (1-2): p. 121-127.

19. Drozdov, A.D. Physical aging in amorphous polymers far below the glass transition temperature. Computational Materials Science, 1999. **15** (4): p. 422-434.

20. ASTM. ASTM D 882-02 : Standard Test Method for Tensile Properties of Thin Plastic Sheeting. American Society for Testing Materials, 2002

21. Barbero, E.J. and K.J. Ford. Equivalent Time Temperature Model for Physical Aging and Temperature Effects on Polymer Creep and Relaxation. Journal of Engineering Materials and Technology, 2004. **126** (4): p. 413-419.

22. Bigg, D.M. A review of positron annihilation lifetime spectroscopy as applied to the physical aging of polymers. Polymer Engineering & Science, 1996. **36** (6): p. 737-743.

23. Drozdov, A.D. A Constitutive Model for Physical Ageing in Amorphous Glassy Polymers. Modelling Simul. Mater. Sci. Eng, 1999. **7** (6): p. 1045-1060.

24. McCaig, M.S. and D.R. Paul. Effect of film thickness on the changes in gas permeability of a glassy polyarylate due to physical agingPart I. Experimental observations. Polymer, 2000. **41** (2): p. 629-637.

25. Montes, H., V. Viasnoff, S. Jurine, and F. Lequeux. Ageing in glassy polymers under various thermal histories. Journal of Statistical Mechanics: Theory and Experiment, 2006. (March): p. P03003.

26. Pasricha, A., D.A. Dillard, and M.E. Tuttle. Effect of physical aging and variable stress history on the strain response of polymeric composites. Composite Science and Technology, 1997. **57** (9-10): p. 1271-1279.

27. Sinko, C.M., A.F. Yee, and G.L. Amidon. The Effect of Physical Aging on the Dissolution Rate of Anionic Polyelectrolytes. Pharmaceutical Research, 1990. **7** (6): p. 648-653.

28. ASTM. ASTM D 2990-01: Standard Test Methods for Tensile, Compressive, and Flexuraly Creep and Creep-Rupture of Plastics. American Society for Testing Materials, 2001

29. Ageeva, M.G. Moisture-resistant film coatings for orally administered medicinal forms. Pharmaceutical Chemistry Journal, 1970. **4** (6): p. 342-346.

30. Anderson, W. and S.A.M. Abdel-Aziz. Ageing Effects in Cast Acrylate-Methacrylate Film. J. Pharm. Pharmacol., 1976. **28** (Suppl: 22P):

31. Chowhan, Z.T., A.A. Amaro, and L.-H. Chi. Comparative Evaluations of Aqueous Film Coated Tablet Formulations by High Humidity Aging. Drug Dev. Ind. Pharm., 1982. **8** (5): p. 713-737.

32. Guo, J.-H. A Theoretical and Experimental Study of the Additive Effects of Physical Aging and Antiplasticization on the Water Permeability of Polymer Film Coatings. Journal of Pharmaceutical Sciences, 1994. **83** (3): p. 447-449.

33. Heinämäki, J.T., V.-M. Lehtola, P. Nikupaavo, and J.K. Yliruusi. The mechanical and moisture permeability properties of aqueous-based hydroxypropyl methylcellulose coating systems plasticized with polyethylene glycol. International Journal of Pharmaceutics, 1994. **112** (2): p. 191-196.

34. Huang, Y. and D.R. Paul. Experimental Methods for Tracking Physical Aging of Thin Glassy Polymer Films by Gas Permeation. J Membrane Sci, 2004. **244** (1-2): p. 167-178.

35. Huang, Y. and D.R. Paul. Effect of Temperature on Physical Aging of Thin Glassy Polymer Films. Macromolecules, 2005. **38** (24): p. 10148-10154.

36. Huang, Y. and D.R. Paul. Physical aging of thin glassy polymer films monitored by gas permeability. Polymer, 2004. **45** (25): p. 8377-8393.

37. Tiemblo, P., J. Guzman, E. Riande, C. Mijangos, and H. Reinecke. Effect of physical aging on the gas transport properties of PVC and PVC modified with pyridine groups. Polymer, 2001. **42** (11): p. 4817-4824.

38. ASTM. ASTM E 96/E 96 M-05: Standard Test Methods for Waer Vapor Transmission of Materials. American Society for Testing Materials, 2005

39. Huang, Y. and D.R. Paul. Physical Aging of Thin Glassy Polymer Films Monitored by Optical Properties. Macromolecules, 2006. **39** (4): p. 1554-1559.

40. Kawana, S. and R.A.L. Jones. Effect of physical ageing in thin glassy polymer films. The European Physical Journal E - Soft Matter, 2003. **10** (3): p. 223-230.

41. Huang, Y., X. Wang, and D.R. Paul. Physical aging of thin glassy polymer films: Free volume interpretation. Journal of Membrane Science, 2006. **277** (1-2): p. 219-229.

42. Chang, G.-W., A.M. Jamieson, Z. Yu, and J.D. McGervey. Physical aging in the mechanical properties of miscible polymer blends. Journal of Applied Polymer Science, 1997. **63** (4): p. 483-496.

43. Kobayashi, Y., W. Zheng, E.F. Meyer, J.D. McGervey, A.M. Jamieson, and R. Simha. Free volume and physical aging of poly(vinyl acetate) studied by positron annihilation. Macromolecules, 1989. **22** (5): p. 2302-2306.

44. Zelko, R., A. Orban, and K. Suvegh. Tracking of the physical ageing of amorphous pharmaceutical polymeric excipients by positron annihilation spectroscopy. Journal of Pharmaceutical and Biomedical Analysis, 2006. **40** (2): p. 249-254.

45. Zelko, R., A. Orban, K. Suvegh, Z. Riedl, and I. Racz. Effect of plasticizer on the dynamic surface tension and the free volume of Eudragit® systems. International Journal of Pharmaceutics, 2002. **244** (1-2): p. 81-86.

46. Cangialosi, D., H. Schut, A. van Veen, and S.J. Picken. Positron Annihilation Lifetime Spectroscopy for Measuring Free Volume During Physical Aging of Polycarbonate. Macromolecules, 2003. **36** (1): p. 142-147.

47. Perera, D.Y. Effect of thermal and hygroscopic history on physical ageing of organic coatings. Progress in Organic Coatings, 2002. **44** p. 55-62.

48. Amighi, K. and A.J. Moës. Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit® RS 30 D film-coated sustained-release theophylline pellets. European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42** (1): p. 29-35.

49. Billa, N., K.-H. Yuen, and K.-K. Peh. Diclofenac release from Eudragit®-containing matrices and effects of thermal treatment. Drug Dev. Ind. Pharm., 1998. **24** (1): p. 45-50.

50. Lin, A.Y., N.A. Muhammad, D. Pope, and L.L. Augsburger. A Study on the Effects of Curing and Storage Conditions on Controlled Release Diphenhydramine HCl Pellets Coated with Eudragit® NE 30 D. Pharm. Dev. Tech., 2003. **8** (3): p. 277-287.

51. Shao, Z.J., L. Moralesi, S. Diaz, and N.A. Muhammadi. Drug Release from Kollicoat® SR 30D-Coated Nonpareil Beads: Evaluation of Coating Level, Plasticizer Type, and Curing Condition. AAPS Pharm. Sci. Tech., 2002. **3** (2).

52. Wesseling, M. and R. Bodmeier. Influence of Plasticization Time, Curing Conditions, Storage Time, and Core Properties on the Drug Release from Aquacoat-Coated Pellets. Pharm. Dev. Tech., 2001. **6** (3): p. 325-331.

53. Amighi, K. and A.J. Moës. Influence of curing conditions on the drug release rate from Eudragit® NE 30 D film coated sustained-release theophylline pellets. S.T.P. Pharma Sci, 1997. **7** (2): p. 141-147.

54. Lin, A.Y. and L.L. Augsburger. Study of Crystallization of Endogenous Surfactant in Eudragit® NE 30 D-Free Films and Its Influence on Drug-Release Properties of Controlled-Release Diphenhydramine HCl Pellets Coated with Eudragit® NE 30 D. AAPS PharmSci., 2001. **3** (2):

55. Bajdik, J., K. Pintye-Hodi, G.J. Regdon, P. Fazekas, P. Szabo-Revesz, and I. Eros. The effect of storage on the behaviour of Eudragit® NE free film. Journal of Thermal Analysis and Calorimetry, 2003. **73** (2): p. 607-613.

56. Wu, C. and J.W. McGinity. Influence of Ibuprofen as a Solid-State Plasticizer in Eudragit® RS 30 D on the Physicochemical Properties of Coated Beads. AAPS Pharm. Sci. Tech., 2001. **2** (4): p. 1-9.

57. Wu, C. and J.W. McGinity. Influence of an Enteric Polymer on Drug Release Rates of Theophylline from Pellets Coated with Eudragit® RS 30 D. Pharm. Dev. Tech., 2003. **8** (1): p. 103-110.

58. Zheng, W. and J.W. McGinity. Influence of Eudragit® NE 30 D Blended with Eudragit® L 30 D-55 on the Release of Phenylpropanolamine Hydrochloride from Coated Pellets. Drug Development and Industrial Pharmacy, 2003. **29** (3): p. 357-366.

59. Maejima, T. and J.W. McGinity. Influence of film additives on stabilizing drug release rates from pellets coated with acrylic polymers. Pharmaceutical Development and Technology, 2001. **6** (2): p. 211-221.

Chapter 2: Research Objectives

2.1 Overall Objectives

The objective of this study was to investigate the effects of water soluble and water insoluble excipients on the mechanisms of stabilization of acrylic films to prevent physical aging. The effect of excipients on the thermal properties, the physical mechanical properties, and water vapor transmission rate of both sprayed and cast films was studied. The mechanism of drug release due to stabilizing excipients was also investigated to examine the stability of dosage forms during storage.

2.2 Supporting Objectives

2.2.1 Investigate the Use of Proteins to Minimize the Physical Aging of Eudragit® RS/RL 30 D Sustained Release Films

The addition of water-soluble, non-ionic excipients that are immiscible with the functional polymer has been shown to stabilize the drug release rate from coated pellets. In this study, the influence of immiscible proteins that exhibited ionic character, albumin and Type B gelatin, were investigated as stabilizing excipients for theophylline pellets coated with Eudragit® RS and RL 30 D. The physico-mechanical properties of sprayed films, thermal properties of cast films, protein influences on the zeta potential and particle size of the dispersions, and the release of proteins from cast films under simulated dissolution conditions were investigated. The effect of temperature and humidity during storage on drug release from coated pellets was studied as well as the influence of pH of the Eudragit® polymeric dispersion on protein-polymer interactions.

2.2.2 Examine the Effect of Silicon Dioxide on Stabilizing Drug Release from Theophylline Pellets Coated with Eudragit® RS/RL 30 D

The addition of a glidant is necessary during the fluidized bed coating of pellets to prevent the sticking of the multi-particulates during the process. Previous work has revealed that when high levels of talc are present in the coating formulation a sustained release profile can be maintained and the dosage forms show good stability upon storage. Also, research in the past has shown that silicon dioxide can be successfully implemented as a glidant for the coating of multi-particulates. The objective of this study was to investigate the influence of three grades of silicon dioxide (Cab-O-Sil® M-5P, Aerosil® 200 VV, and Aeroperl® 300) on the physical aging and drug release of theophylline pellets coated with Eudragit® RS/RL 30 D. Scanning electron microscopy was employed to examine the distribution of silicon dioxide in the film matrix. The water vapor permeability and physico-mechanical properties of cast films were investigated as was the influence of storage conditions on the drug release from coated pellets.

2.2.3 Study the Addition of Ethylcellulose as an Agent to Maintain the Physical Stability of Eudragit® NE 30 D Coated Theophylline Pellets

Past research has shown that the stability of Eudragit® NE 30 D film-coated dosage forms can be enhanced by the addition of a miscible, high glass transition temperature, enteric polymer. The aim of this study was to investigate how the addition of ethylcellulose (a non-enteric, high Tg polymer) affected the stability of Eudragit® NE 30 D films and film-coated theophylline pellets. The miscibility between the two polymers was probed with the use of modulated differential scanning calorimetry. The effect of Ethocel® particle size and molecular weight on the drug release was investigated as was the influence of fine particle ethylcellulose on the physical stability of coated pellets and the physico-mechanical properties and water vapor permeability of sprayed films. It was hypothesized that the addition of the substantially immiscible ethylcellulose

would decrease the degree of coalescence of the acrylic polymer and stabilize the drug release rate from coated pellets stored at both room and accelerated conditions.

2.2.4 Investigate the Influence of Blends of Acrylic Polymers on the Physical Aging of Theophylline Pellets Coated with Eudragit® NE 30 D/RS 30 D

The use of a plasticizer is necessary to decrease the glass transition temperature of a polymer, as well as lower the minimum film formation temperature. The objective of this study was to investigate the effect of blending Eudragit® RS 30 D with Eudragit® NE 30 D and examine the effect the polymer blend had on the drug release rate and physical stability of coated pellets. The miscibility of the two polymers was examined as were the physico-mechanical properties and water vapor permeability of sprayed films. It was hypothesized that the addition of Eudragit® RS 30 D would stabilize the drug release rate by increasing the glass transition temperature of the blend above storage conditions to the point that films would be formed and retain good physical stability during storage.

Chapter 3: An Investigation of the Use of Proteins to Minimize the Physical Aging of Eudragit® Sustained Release Films[2]

Abstract:

The objective of this study was to investigate the influence of two proteins, albumin and Type B gelatin, on the physical aging of Eudragit® RS 30 D and RL 30 D coated theophylline pellets. The physico-mechanical properties of sprayed films, thermal properties of cast films, influence of proteins on the zeta potential and particle size of the dispersion, and the release of proteins from cast films under simulated dissolution conditions were investigated. The release rate of theophylline decreased significantly over time from pellets coated with an acrylic dispersion containing 10% albumin when there was no acidification of the acrylic dispersion; however, when pellets were coated with an acidified Eudragit®/albumin dispersion, the theophylline release rate was stable for dosage forms stored in the absence of humidity. The drug release rate was faster for pellets coated with acrylic dispersions containing 10% gelatin compared to the albumin–containing formulations. When sprayed films were stored at 40°C/75% RH, the water vapor permeability decreased significantly for both Eudragit® films and those containing Eudragit® and albumin; however, there was no significant change in this parameter when 10% gelatin was present. Albumin was released from the acrylic films when the pH of the dissolution media was below the isoelectric point of the protein while no quantitative release of gelatin was observed in pH 1.2 or 7.4 media. The effect of gelatin to prevent the decrease in drug release rate was due to stabilization in water vapor permeability of the film. Acidification of the polymeric dispersion resulted in electrostatic repulsive forces between albumin and the acrylic polymer, which stabilized the drug release rate

[2] Significant portions of this chapter were taken from: Kucera, S.A., W. Zheng, N. Shah, A. Malick, M. Infeld, and J.W. McGinity. The Use of Proteins to Minimize the Physical Aging of Eudragit® Sustained Release Films. *Drug Dev. Ind. Pharm.* 33 (7), pp. 717-726. (2007)

when the dosage forms were stored in aluminum induction sealed containers at both 40°C/75% RH and 25°C/60% RH.

3.1 INTRODUCTION

The use of aqueous polymeric dispersions for film coating solid dosage forms has gained in popularity due to increased government regulations, as well as the safety issues associated with the use of organic solvents in film coating processes. The film formation mechanism, however, is more complex with latex and pseudolatex dispersions than with organic solvent systems. One problem prevalent in aqueous latex coating systems is physical aging of the polymeric film during storage. This results from the further coalescence of latex particles and a decrease in void volume of the polymeric film as the polymer relaxes towards an equilibrium state [1-4]. Physical aging of film coatings will generally result in a decrease in the drug release rate from the coated dosage form [1, 2, 4-7].

Diffusion-controlled drug release can be described by Fick's Law, as seen in equation 3.1, where Q is the quantity of drug released in time t, D is the diffusion coefficient of the drug, S is the area of diffusion, C_1 is the drug concentration in the dosage form, C_2 is the drug concentration in the dissolution media, and h is the film thickness.

$$Q = \frac{DS(C_1 - C_2)t}{h} \qquad \text{(Eq. 3.1)}$$

$$D = \frac{D_w(e)}{\tau} \qquad \text{(Eq. 3.2)}$$

Fick's Law is related to physical aging by the Iyer equation, which is described by equation 3.2. Here, D is the diffusion coefficient of the drug, D_w is the diffusion coefficient of the drug in water, e is the film porosity, and τ is the film tortuosity. There is a decrease in film porosity and void volume and an increase in tortuosity as

coalescence of the colloidal particles continues during storage, which results in a decrease in the diffusion coefficient. This decrease in the diffusion coefficient is responsible for the decrease in dissolution rate during storage of film coated dosage forms [7].

There have been several approaches published in the literature to prevent the physical aging of dosage forms coated with colloidal aqueous dispersions. Amighi and Moës [1] reported that as the plasticizer concentration was increased, the degree of coalescence of the latex particles also increased and that pellets coated with a polymeric dispersion containing less plasticizer showed more pronounced aging effects. The time required to achieve a stabilized drug release rate was also dependent on the curing temperature, with stable films obtained faster when cured at higher temperatures. Maejima and McGinity [6] showed that thermal treatment along with high concentrations of micronized talc stabilized drug release from pellets coated with Eudragit® RS/RL 30 D plasticized with TEC. The addition of a high glass transition temperature polymer to an acrylic dispersion to stabilize drug release rates was reported by Wu and McGinity [3]. The addition of Eudragit® L 100-55 to Eudragit® RS 30 D resulted in a stable drug release rate in an acidic medium when coated pellets were stored under accelerated conditions. At a higher pH, an increase in drug release was seen due to pore formation as the enteric polymer dissolved. Similarly, Eudragit® L 30 D-55 was shown to stabilize drug release from pellets coated with Eudragit® NE 30 D [4]. Inclusion of a hydrophilic polymer, hydroxyethylcellulose (HEC), to Eudragit® RS 30 D dispersions stabilized the drug release rates during storage due to the formation of an immiscible secondary phase surrounding the colloidal particles which interfered with further coalescence of the colloidal acrylic particles [7]. Lastly, ionic electrostatic interactions have also been investigated to minimize physical aging effects in aqueous-based polymeric dispersions [8].

The objective of the present study was to investigate the influence of albumin and Type B gelatin on the physical aging of theophylline pellets coated with Eudragit® RS/RL 30 D. The physico-mechanical properties of sprayed films, thermal properties of cast films, protein influences on the zeta potential and particle size of the dispersions, and the release of proteins from cast films under simulated dissolution conditions were investigated. The effect of temperature and humidity during storage on drug release from coated pellets was studied as well as the influence of pH of the Eudragit® polymeric dispersion on protein-polymer interactions.

3.2 MATERIALS AND METHODS

3.2.1 Materials

Eudragit® RS 30 D and RL 30 D dispersions were donated by Degussa (Parsippany, NJ, USA). Anhydrous theophylline, fraction V heat-shock bovine serum albumin (BSA), Type B gelatin, and lactose monohydrate were all purchased from Spectrum Chemical (Gardena, CA, USA). Polyvinylpyrrolidone (Kollidon® K-30) was donated by the BASF Corp. (Mount Olive, NJ, USA). Microcrystalline cellulose (Avicel® PH-101) was donated by the FMC Corp. (Newark, DE, USA). Altalc 500V was supplied by Luzenac America, Inc. (Englewood, CO, USA). Triethyl citrate (TEC) was donated by Morflex, Inc. (Greensboro, NC, USA). Hypromellose (Pharmacoat® 603) was donated by Shin-Etsu Chemical Co. (Tokyo, JP).

3.2.2 Methods

3.2.2.1 Preparation of Core Pellets

Anhydrous theophylline (25%), lactose monohydrate (45%) and microcrystalline cellulose (25%) were passed through a 30-mesh sieve and then mixed in a twin-shell blender for 15 minutes. A 12.5% w/v aqueous solution of polyvinylpyrrolidone (equivalent to 5% in the final formulation) was used as a binder in the wet-massing process. The wet mass was extruded using a LCI Benchtop Granulator (Tokyo, JP) at a

rotation blade speed of 50 rpm. The extrudates were spheronized at 1000 rpm for 2 minutes using a Caleva Model 120 Spheronizer (Dorset, UK). The pellets were sieved after drying for 24 hours at 40°C, and the 16-20 mesh fraction was used for the coating trials.

3.2.2.2 Preparation of Coating Dispersions

Eudragit® RS 30 D (95% dry polymer weight) and Eudragit® RL 30 D (5% dry polymer weight) were combined with TEC (15%, based on the total dry polymer weight) and the protein solution (10%, based on the total dry polymer weight) and equilibrated with slow agitation for two hours under ambient conditions. Albumin was mixed with deionized water to yield a 3.75% solution prior to addition to the polymer dispersion. Gelatin was dissolved in deionized water (40°C) to yield a 1% solution and allowed to cool to room temperature before addition to the acrylic dispersion. Talc (50%, based on the total dry polymer weight) was dispersed in 150 ml of deionized water using a POLYTRON (Brinkmann Instruments, Westbury, NY, USA) and then added to the acrylic dispersion for a further 15 minutes of agitation.

3.2.2.3 Film Coating

A 250-g batch containing 50% theophylline pellets and 50% non-pareils of the same size fraction was placed in a Strea-1 fluidized-bed coater (Aeromatic-Fielder, Bubendorf, SW), and the polymeric dispersion was applied with a peristaltic pump through a 1.2 mm nozzle until the film weight gain of the pellets was 15% theoretical gain. The inlet temperature was 40-42°C and the outlet temperature was 32-35°C. To avoid pellet agglomeration, the dispersion was applied at a rate of 1 g/min until a weight gain of 2.5% had been reached and then increased to 3 g/min. The atomizing air pressure of the unit was 25 psi. The polymeric dispersion was stirred continuously throughout the coating process to prevent the sedimentation of the dispersed solids.

To prevent agglomeration and sticking of the pellets during storage, a 2% total weight gain of hypromellose (Pharmacoat® 603) was applied to the coated pellets from a 5% w/w aqueous solution. The inlet temperature was 45°C, the outlet temperature 40°C, and the spray rate was 2 g/min. The pellets were then placed in a 40°C oven for 12 hours to remove residual moisture.

3.2.2.4 Free Film Preparation

Films were prepared by either a cast or spray method. For the cast method, the coating dispersion without talc was cast onto a Teflon plate and dried for 72 hours under ambient conditions. These films were used in experiments to study protein release from films as well as for thermal experiments. The second method to prepare the free films was a spray technique that was similar to a previously described method used by Obara and McGinity [9]. Films were sprayed onto a Teflon sheet attached to a cylinder rotating at 44 rpm. An infrared lamp was used to maintain the sprayed film in the temperature range of 22–28°C. The atomizing air pressure was 0.50 kg/cm^2. The spray rate was maintained at 2 g/min and delivered through the 1.2 mm nozzle. Formulations for the sprayed films were the same as those used in the coating trials.

3.2.2.5 Thermal Analysis of Films

The thermal properties of the cast films were determined by modulated differential scanning calorimetry (MDSC) (TA Instruments, New Castle, DE, USA). The films were cast from aqueous dispersions in the same ratios that were used for the film-coating trials. Film samples of 10–15 mg were weighed into aluminum pans and then sealed. The samples were analyzed in a nitrogen atmosphere with a heating rate of 3°C/min over a temperature range of -20–110°C with a modulation rate of 1°C/min. The glass transition temperature was determined as the midpoint of the transition using Modulated DSC Analysis V1.1A software.

3.2.2.6 Physico-Mechanical Testing

Stress-strain experiments with films prepared by the spray method were performed using an Instron Model 4201 according to ASTM guideline D 882-02 [10]. Films were cut into 100 mm x 10 mm strips. Thickness was measured using a Starrett® No. 723 digital micrometer (L.S. Starrett, Athol, MA) and the average of seven different measurements along the length of the film was determined. A 1000 N load cell was mounted on the instrument. The distance between the grips was 60 mm, the load range was 50 N, and the crosshead speed was set at 10 mm/min. The tensile strength at break was determined. This parameter was calculated using the following formula:

$$Tensile\ Strength\ at\ Break = \frac{Load\ at\ Break}{Minimum\ Cross\text{ - }sectional\ Area} \qquad \text{(Eq. 3.3)}$$

3.2.2.7 Water Vapor Transmission Rate

The water vapor transmission rate of the sprayed films was determined according to guidelines set forth in ASTM E 96-00 [11] using the desiccant method, as previously described by Zheng and McGinity [7]. The thickness of each film was determined using a Starrett® No. 723 digital micrometer (L.S. Starrett, Athol, MA) by measuring eight points along the circumference of a circular sample of sprayed film and averaging the values. The film sample was secured to the open mouth of an aluminum permeability cup (4 cm inner diameter and 3 cm depth) containing 20 g of Drierite® desiccant. The permeability cups were accurately weighed, placed in a humidity chamber at 23°C/80% RH, and periodically reweighed over seven days to determine the weight gain. The water vapor transmission rate (*WVT*) and permeability (*P*) were calculated using the following equations [11]:

$$WVT = (G/t)/A \qquad \text{(Eq. 3.4)}$$

$$P = \frac{WVT}{S} \times (R_1 - R_2) \times d \qquad \text{(Eq. 3.5)}$$

where G is the weight change, t is the time during which G occurred, A is the test area (cup mouth area), S is the saturation vapor pressure at test temperature, R_1 and R_2 are the relative humidity in the test chamber and inside the cup, respectively, and d is the thickness of the film.

3.2.2.8 Particle Size and Zeta Potential Analysis

The particle size and zeta potential of the colloidal particles in the latex dispersion following the addition of either albumin or gelatin were determined using a Zeta Plus Zeta Potential Analyzer (Brookhaven Instruments Corp.). The dispersion samples were diluted with deionized water, added to a cuvette, and allowed to stabilize at 25°C. A refractive index of 1.59 was used for particle size studies.

3.2.2.9 Viscosity Measurements

The viscosity of the dispersions was measured using a Brookfield DV-I+ viscometer (Brookfield Engineering, USA) with an H1 spindle size at 30 ±1°C and 100 rpm (n=3). The viscosity of a 30% w/v Eudragit® RS/RL 30 D blend (95:5) was used as a control. For measurements of albumin-containing dispersions, 10% protein (based on the dry polymer weight of the acrylic) was added as a solution while being stirred with a magnetic stir bar. After all of the protein solution had been added, viscosity measurements proceeded and data was collected after 3 minutes.

3.2.2.10 Protein Release from Free Films

The dissolution rate of the protein from cast films containing either albumin or Type B gelatin was studied. A 500 mg sample of cast film (containing approximately 40 mg of protein) was placed in scintillation vials containing 20 ml of either pH 1.2 (0.1 N HCl) or pH 7.4 (50 mM) phosphate buffer previously heated to a temperature of 37°C. The vials were placed in an enclosed, temperature controlled (37°C) orbital shaker and

agitated at a rate of 100 rpm. Samples of 1 ml were removed at 1-, 3-, and 6-hour intervals. The protein assay was performed using a DC Protein Assay kit (BIO-RAD) with a reaction time of 15 minutes and a λ_{max} of 750 nm using a μQuant 96-Well Plate Reader (Bio-Tek Instruments, Inc.).

3.2.2.11 Stability Testing and In Vitro Drug Release

Coated pellets were placed in polyethylene bottles and kept either open to the environment or hermetically sealed with aluminum induction seals with desiccant inside and then stored at 25°C/60% RH and 40°C/75% RH for up to 3 months. The percent water absorbed from the coated pellets was analyzed by heating the pellets to 110°C for a period of 30 minutes using an AND MF-50 Moisture Analyzer (DSC, Inc., Encino, CA, USA). Dissolution was performed according to the United States Pharmacopeia (USP) 27 Apparatus II (Vankel VK 7000, Cary, NC, USA) over a 12-hour period in 900 ml of pH 7.4 (50 mM) phosphate buffer. The paddle speed was 50 rpm and the temperature of the media was maintained at 37±0.2°C.

300 mg of coated pellets was added to each dissolution vessel and 5-ml samples were removed by a Vankel 8000 Autosampler (Cary, NC, USA) at 1-, 2-, 3-, 4-, 5-, 6-, 8-, 10-, and 12-hour intervals. An infinity sample was obtained by mixing with a high-shear homogenizer (POLYTRON, Brinkmann Instruments, Westbury, NY, USA) and then analyzed for drug content. All dissolution tests were performed in triplicate.

The theophylline content of each sample was analyzed using high performance liquid chromatography (HPLC). The samples were filtered through a 0.45 μm nylon filter. A volume of 4 ml was allowed to pass through the filter with the remaining 1 ml being used for analysis after filtration. Analysis was performed using a Waters® 717 Plus Autosampler, two 515 HPLC pumps, a column heater set to 30°C, and 996 PDA. Results were calculated using Empower Pro software. A Metachem® Intertsil ODS-3 3 μm column (150 x 4.6 mm) was used for separation with an analyte retention time of 2.8 minutes. The amount of theophylline released was computed by taking the analyte peak

area, comparing this to the peak area of the infinity time point sample, and multiplying by 100 to obtain a percentage of theophylline released at each time point.

3.3 RESULTS AND DISCUSSION

The water vapor permeability of Eudragit® RS/RL 30 D sprayed films containing 15% TEC and either 10% albumin or gelatin is shown in Table 3.1. The films were stored at 40°C/75% RH in open containers. When comparing initial values between the albumin and gelatin formulations, no significant difference was observed; however, there was a significant difference (single factor ANOVA, $p<0.05$) between the two protein-containing formulations and the Eudragit® RS/RL 30D films. This difference was due to the hydrophilicity of the proteins. During storage, a significant decrease in this parameter was seen in the Eudragit® RS/RL 30 D films as well as those containing albumin which was attributed to a decrease in void space and further densification of the film. The films containing gelatin exhibited no significant change in water vapor permeability after storage and the significance of these results will become clear during the discussion of the results from the dissolution studies.

The tensile strength of sprayed films stored for 1 month at 40°C/75% RH is also shown in Table 3.1. Changes in tensile strength help explain the physical aging phenomenon in polymeric systems. The further coalescence of polymeric latex particles causes an increase in tensile strength, which was reported in previous studies [7]. All films exhibited significant increases in tensile strength during storage.

Plasticizers weaken polymeric intermolecular interactions and increase the flexibility of the polymer [12, 13], resulting in an increase in free-film elongation and a decrease in tensile strength. A common method used to evaluate plasticizer effectiveness is by determination of the glass transition temperature (T_g). The T_g was investigated to determine if plasticization would account for the mechanical changes observed in the protein-containing films. The presence of either protein in the acrylic film showed no significant impact on the glass transition temperature in the presence or absence of

triethyl citrate, indicating that neither protein plasticized the acrylic polymer and that both proteins were immiscible with the polymer (Table 3.2).

Monodisperse latex particles have previously been used to bind and separate albumin in biological applications [14]. This attraction was found to be due to the presence of hydrogen bonding between the latex particles and the albumin molecules. Since albumin is an amphoteric protein, the pH of the environment will determine the charge on the molecule. At a pH above the isoelectric point of the protein, the molecule carries a net negative charge, while at a pH below the isoelectric point, albumin will carry a net positive charge. Since the pH of the acrylic dispersion is in the range of 5.0-5.2 and the isoelectric point of albumin is 4.7 [15], Eudragit® RS/RL 30 D, which contains positively charged quaternary ammonium functional groups, will interact with the negatively charged albumin molecules and affect the film formation mechanism.

During preparation of the coating dispersion, the acrylic dispersion exhibited a significant increase (single factor ANOVA, $p<0.05$) in viscosity from 16.57 (±1.07) cps to 56.67 (±1.62) cps when the albumin solution was added. These findings were attributed to the agglomeration or binding between albumin and acrylic particles. These results are supported by Omari and colleagues [8] who demonstrated that quaternary ammonium groups coupled with a chloride exhibit 100% dissociation of the chloride ion in the pH range of 1-8. As these functional groups are positively charged, they are free to interact with negatively charged molecules in solution. Particle size analysis was performed on an Eudragit® RS/RL 30 D dispersion adjusted to pH 2.5 by the addition of 0.1 N HCl [16] and also at the pH of the dispersion as received (pH ≈ 5.0). An increase in mean particle size of 40 nm (initial size 125 nm) was seen when albumin was added to the dispersion (pH≈5.0) while no increase in particle size was observed when albumin was placed in the pH 2.5 dispersion.

The effect of protein addition on the zeta potential of the latex dispersion can be seen in Table 3.3. The zeta potential is useful for determining how particles interact with

one another and for predicting the stability of dispersed colloid systems. Inter-particle reactions are likely to occur when the particles are of a different charge, with these reactions mostly being coagulation [17]. The zeta potential of the Eudragit® dispersion in the current study was comparable to results reported by others [16]. When an albumin solution was added to the acrylic dispersion, however, a significant decrease in zeta potential was noted, indicating a decrease in colloidal stability. At the lower pH, below the isoelectric point of albumin, colloidal stability was maintained as evidenced by no change in the zeta potential. These findings were attributed to an electrostatic repulsion between the positively charged protein and the polymer.

The influence of albumin on the theophylline release rate from coated pellets was studied. When stored at 40°C and 75% relative humidity in open containers over three months, there was a significant decrease in drug release from pellets coated with an acrylic dispersion (pH≈5.0) containing albumin (Figure 3.1). The drug release rate from the coated pellets had not equilibrated after three months of storage, and only 42% of the total theophylline was released after a period of 12 hours. This decrease was in agreement with the changes observed in the physico-mechanical and water vapor permeability properties of the sprayed films as noted in Table 3.1. When the pH of the Eudragit® dispersion was adjusted to 2.5 by the addition of 0.1 N HCl, a smaller decrease in drug release rate was observed during storage, but physical aging was still evident (Figure 3.2). Albumin, being negatively charged at a pH above its isoelectric point, interacted with the acrylic polymer and depressed the drug release rate when compared with an acidified dispersion.

When theophylline pellets coated with the acrylic-albumin dispersion were stored in hermetically sealed HDPE containers with desiccant, the coated pellets stored at 40°C/75% RH (Figure 3.3) and 25°C/60% RH (Figure 3.4) showed no change in drug release over time. The decrease in drug release rate seen in Figure 3.1 and Figure 3.2 was due to a combination of protein-polymer interaction and humidity causing a decrease in

the permeability of the film, rather than the temperature at which the dosage forms were stored. The absorption of water due to highly humid storage environments has been shown to increase the physical aging of films [1, 3, 5, 18]. Water acts as a plasticizer and can cause further coalescence of the film during storage, leading to a decrease in drug release. Both formulations containing 10% albumin and gelatin showed an increase in water content of 4.35% and 3.55%, respectively, during storage over 1 month at 40°C and 75% relative humidity in open containers.

The addition of gelatin to the acrylic dispersion produced an opposite effect on drug release when compared to albumin. As seen in Figure 3.5 and Figure 3.6, film-coated dosage forms showed no change in the dissolution rate at 40°C and 75% relative humidity when stored in open containers and closed containers. The complete coalescence of latex particles can only be achieved when polymeric molecules located at the interface between adjacent particles interpenetrate as a result of viscous flow. The addition of an immiscible hydrophilic polymer resulted in the formation of an incompatible phase around the colloidal latex particles, which prevented complete coalescence and interdiffusion of polymer chains [7]. Stabilization of drug release in the gelatin containing formulations can be explained by the water vapor permeability results which showed no change during storage after 1 month at 40°C/75% RH.

The theophylline release was faster from pellets coated with an acrylic-gelatin dispersion in comparison to those coated with an acrylic-albumin dispersion. One potential reason for these results may be related to pore formation in the film due to solvation of the protein during dissolution. This was studied indirectly by investigating the amount of protein released in the media from cast films of Eudragit® RS/RL 30 D (95:5), 15% TEC, and either 10% albumin or Type B gelatin. The release of albumin in the dissolution media was found to be a function of pH, as seen in Figure 3.7. At a media pH of 1.2, albumin was released into the dissolution media. The acidic environment changed the net charge of the albumin molecule to positive, resulting in albumin release

from the film due to charge-charge repulsion with the quaternary ammonium group of the acrylic polymer. The drug release in 0.1 N HCl was faster with 100% of theophylline being released within 2-3 hours (data not shown). At pH 7.4, a detectable amount of albumin was released in the dissolution media; however, this amount was below the limits of quantification in the assay used. At this pH, the film was in an environment above the isoelectric point of the albumin, retaining the net negative charge and thus keeping the albumin bound to the acrylic polymer. When latex films containing gelatin were investigated, the amount of gelatin free in solution was below the limits of detection at both pH 1.2 and 7.4. These data show that gelatin did not dissolve to create pores through which theophylline would diffuse, but rather formed diffusional domains due to entanglement of the high molecular weight polypeptide with the acrylic polymer which altered the rate of diffusion of the drug through the membrane. This is further supported by the lag time in drug release rate seen in Figure 3.1, Figure 3.2, Figure 3.3, and Figure 3.4 and the increased rate of theophylline release seen in Figure 3.5 and Figure 3.6. The acrylic latex is a copolymer of acrylic and methacrylic acid esters with hydrophilic quaternary ammonium groups, which are responsible for the polymer's ability to swell when exposed to aqueous media [7]. The initial delay of drug release in formulations coated with acrylic-albumin dispersions shows that the polymer was the rate controlling membrane for drug release. Conversely, the faster release of theophylline from gelatin-containing formulations was due to the gelatin phase of the coating being responsible for the increase in the drug release rate.

3.4 CONCLUSION

The addition of 10% Type B gelatin to Eudragit® RS/RL 30 D films plasticized with 15% TEC stabilized theophylline release profiles, with no change in the release rate for pellets stored at 40°C and 75% relative humidity in both open and closed containers, with the mechanism being due to the stabilization of the water vapor permeability parameter. The hydrophilic gelatin molecule resulted in films which exhibited a steady

water vapor transmission rate and faster release of the model drug from the coated dosage forms compared to those containing albumin. The absence of gelatin in the dissolution media during protein release studies confirmed that the increase in drug release rate resulted from gel domains which facilitated diffusion of theophylline rather than the formation of pores in the film. Complexation between albumin and the colloidal latex particles was due to changes in pH of both dispersion and dissolution media. Humidity was a factor in the stability of theophylline pellets coated with albumin-containing acrylic dispersions. A decrease in both the physico-mechanical properties and water vapor permeability of these films led to a decrease in theophylline release when stored in open containers at high humidity.

3.5 REFERENCES

1. Amighi, K. and A.J. Moës. Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit® RS 30 D film-coated sustained-release theophylline pellets. European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42** (1): p. 29-35.

2. Frisbee, S.E., K.A. Mehta, and J.W. McGinity. Processing Factors that Influence the In Vitro and Performance of Film-Coated Drug Delivery Systems. Drug Delivery Technology, 2002. **21** (1): p. 72-76.

3. Wu, C. and J.W. McGinity. Influence of an Enteric Polymer on Drug Release Rates of Theophylline from Pellets Coated with Eudragit RS 30 D. Pharm. Dev. Tech., 2003. **8** (1): p. 103-110.

4. Zheng, W. and J.W. McGinity. Influence of Eudragit® NE 30 D Blended with Eudragit® L 30 D-55 on the Release of Phenylpropanolamine Hydrochloride from Coated Pellets. Drug Development and Industrial Pharmacy, 2003. **29** (3): p. 357-366.

5. Amighi, K. and A.J. Moës. Influence of curing conditions on the drug release rate from Eudragit NE 30 D film coated sustained-release theophylline pellets. S.T.P. Pharma Sci, 1997. **7** (2): p. 141-147.

6. Maejima, T. and J.W. McGinity. Influence of film additives on stabilizing drug release rates from pellets coated with acrylic polymers. Pharmaceutical Development and Technology, 2001. **6** (2): p. 211-221.

7. Zheng, W., D. Sauer, and J.W. McGinity. Influence of hydroxyethylcellulose on the drug release properties of theophylline pellets coated with Eudragit® RS 30 D. European Journal of Pharmaceutics and Biopharmaceutics, 2005. **59** (1): p. 147-154.

8. Omari, D.M., A. Sallam, A. Abd-Elbary, and M. El-Samaligy. Lactic acid-induced modifications in films of Eudragit RL and RS aqueous dispersions. International Journal of Pharmaceutics, 2004. **274** (1-2): p. 85-96.

9. Obara, S. and J.W. McGinity. Properties of Free Films Prepared from Aqueous Polymers by a Spraying Technique. Pharmaceutical Research, 1994. **11** (11): p. 1562-1567.

10. ASTM. ASTM D 882-02 : Standard Test Method for Tensile Properties of Thin Plastic Sheeting. - American Society for Testing Materials, 2002

11. ASTM. ASTM E 96-00: Standard Test Methods for Water Vapor Transmission of Materials. 2000.

12. Gutierrez-Rocca, J.C. and J.W. McGinity. Influence of Water-Soluble and Insoluble Plasticizers on the Physical and Mechanical-Properties of Acrylic Resin Copolymers. International Journal of Pharmaceutics, 1994. **103** (3): p. 293-301.

13. Wu, C.B. and J.W. McGinity. Non-traditional plasticization of polymeric films. International Journal of Pharmaceutics, 1999. **177** (1): p. 15-27.

14. Yoon, J.-Y., H.-Y. Park, J.-H. Kim, and W.-S. Kim. Adsorption of BSA on Highly Carboxylated Microspheres – Quantitative Effects of Surface Functional Groups and Interaction Forces. J. Colloid Interf. Sci., 1996. **177** (2): p. 613-620.

15. Friedli, G.-L., Interaction of Deaminated Soluble Wheat Protein with Other Food Proteins and Metals. 1996, University of Surrey.

16. Nyamweya, N., K.A. Mehta, and S.W. Hoag. Characterization of the interactions between polymethacrylate-based aqueous polymeric dispersions and aluminum lakes. J. Pharm. Sci., 2001. **90** (12): p. 1937-1947.

17. Nyamweya, N., K.A. Mehta, and S.W. Hoag. Film coating with aqueous latex dispersions: general considerations for formulating with pigments. Pharm. Tech., 2001. (Yearbook): p. 8, 10-12, 26.

18. Wu, C.B. and J.W. McGinity. Influence of relative humidity on the mechanical and drug release properties of theophylline pellets coated with an acrylic polymer containing methylparaben as a non-traditional plasticizer. European Journal of Pharmaceutics and Biopharmaceutics, 2000. **50** (2): p. 277-284.

3.6 TABLES

Formulation	WVP ($g/Pa \cdot s \cdot m^2$) x 10^{-7}	TSB (10^6 Pa)
Eudragit® RS/RL 30 D with 15% TEC, t_0	2.28 ± 0.06	7.49 ± 0.31
Eudragit® RS/RL 30 D with 15% TEC, t_{1mo}	1.95 ± 0.06	7.95 ± 0.35
Eudragit® RS/RL 30 D, 15% TEC, 10% Albumin, t_0	2.76 ± 0.19	4.91 ± 0.53
Eudragit® RS/RL 30 D, 15% TEC, 10% Albumin, $t_{1\ mo.}$	1.99 ± 0.19	9.09 ± 1.11
Eudragit® RS/RL 30 D, 15% TEC, 10% Gelatin, t_0	**2.74 ± 0.17**	5.40 ± 0.77
Eudragit® RS/RL 30 D, 15% TEC, 10% Gelatin, $t_{1\ mo.}$	**2.47 ± 0.17**	14.12 ± 1.20

NOTE: Bolded values indicate no significant change when analyzed by single factor ANOVA with a p value of 0.05.

Table 3.1 Effect of time on water vapor permeability (WVP) and tensile strength at break (TSB) of Eudragit® RS/RL 30 D films containing 15% TEC as a plasticizer and either 10% BSA or Type B Gelatin stored at 40°C/75% RH in open containers. (Kucera, et al. *Drug Dev. Ind. Pharm.* Vol. 33 Issue 7 pp. 717-726)

Formulation	Tg (°C)
Eudragit® RS/RL	**52.08**
Eudragit® RS/RL 30D, 10% Albumin	**54.12**
Eudragit® RS/RL 30D, 10% Type B Gelatin	**51.87**
Eudragit® RS/RL 30D, 15% TEC	**29.88**
Eudragit® RS/RL 30D, 15% TEC, 10% Albumin	**31.17**
Eudragit® RS/RL 30D, 15% TEC, 10% Type B Gelatin	**28.01**

Table 3.2 The effect of protein addition on the glass transition of Eudragit® RS/RL 30 D cast films. (Kucera, et al. *Drug Dev. Ind. Pharm.* Vol. 33 Issue 7 pp. 717-726)

Formulation	***pH 5.2***	***pH 2.5***
	ζ Potential (std. error)	**ζ Potential (std. error)**
Eudragit® RS/RL 30 D	48.35 (3.25)	49.70 (2.97)
Eudragit® RS/RL 30 D containing 10% Albumin	32.47 (2.51)	49.83 (1.93)
Eudragit® RS/RL 30 D containing 10% Type B Gelatin	49.63 (3.45)	46.75 (3.15)

Table 3.3 The effect of protein addition on the ζ potential (in mV) of Eudragit® RS/RL 30 D dispersions. (Kucera, et al. *Drug Dev. Ind. Pharm.* Vol. 33 Issue 7 pp. 717-726)

3.7 FIGURES

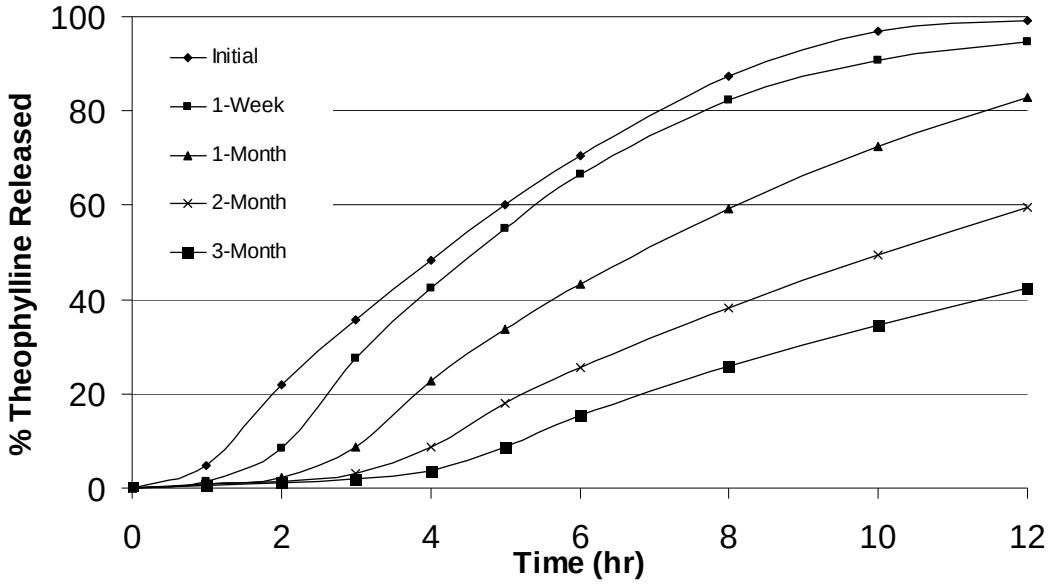


Figure 3.1 The influence of albumin on the release of theophylline from pellets coated with Eudragit® RS/RL 30 D (15% W.G.) containing 10% albumin and stored at 40°C/75% RH in open containers (n=3). (Kucera, et al. *Drug Dev. Ind. Pharm.* Vol. 33 Issue 7 pp. 717-726)

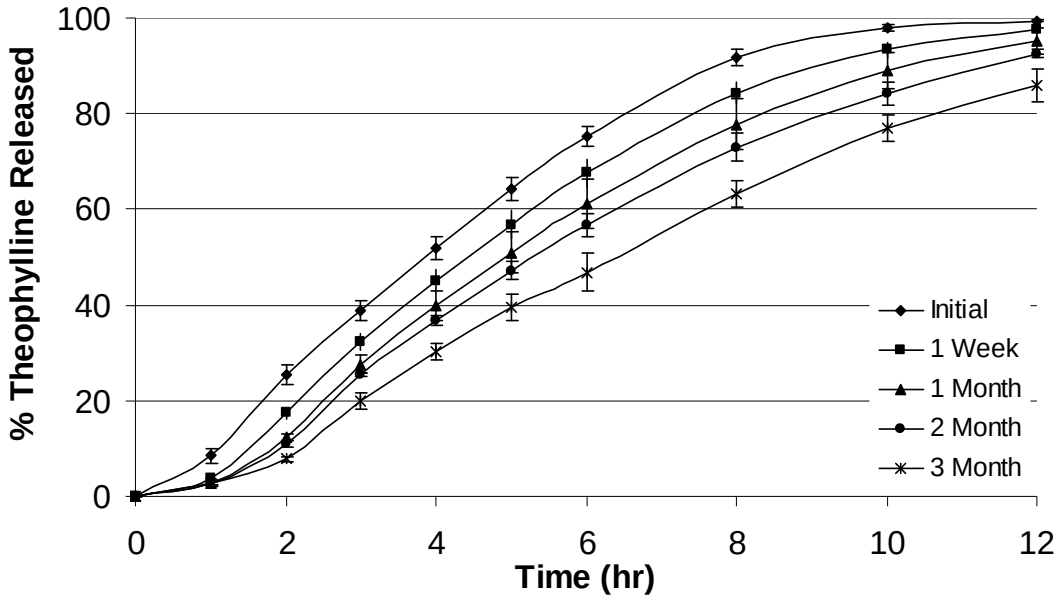


Figure 3.2 The influence of dispersion pH (2.5) on the release of theophylline from pellets coated with Eudragit® RS/RL 30 D (15% WG) containing 10% albumin and stored at 40°C/75% RH in open containers (n=3). (Kucera, et al. *Drug Dev. Ind. Pharm.* Vol. 33 Issue 7 pp. 717-726)

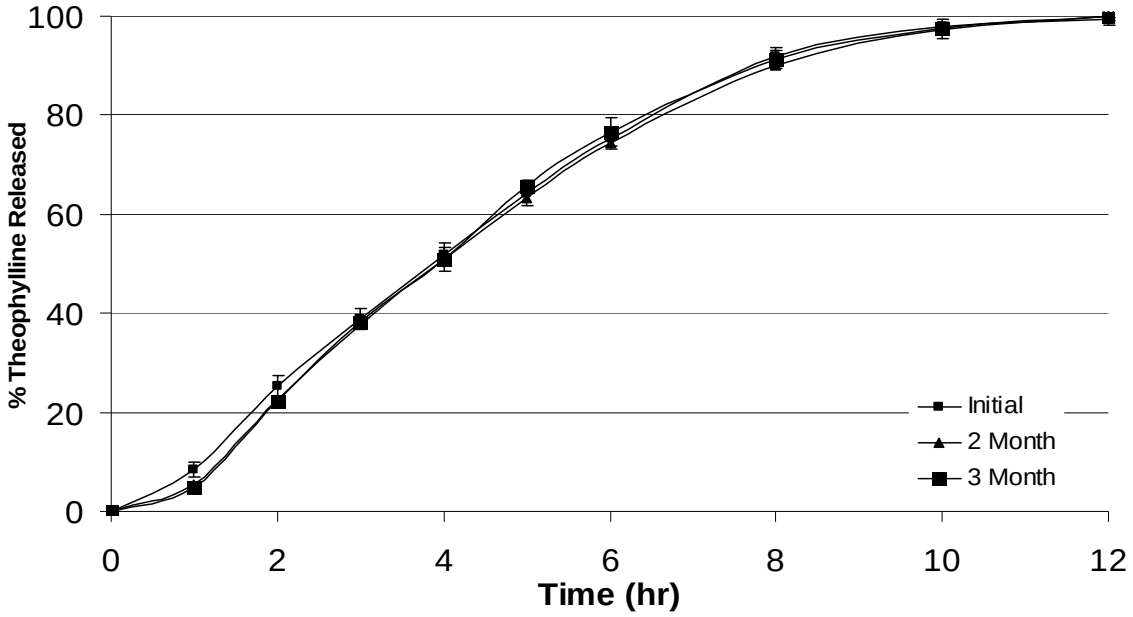


Figure 3.3 The influence of dispersion pH (2.5) on the release of theophylline from pellets coated with Eudragit® RS/RL 30 D (15% WG) containing 10% albumin and stored at 40°C/75% RH in hermetically sealed HDPE containers with desiccant (n=3). (Kucera, et al. *Drug Dev. Ind. Pharm.* Vol. 33 Issue 7 pp. 717-726)

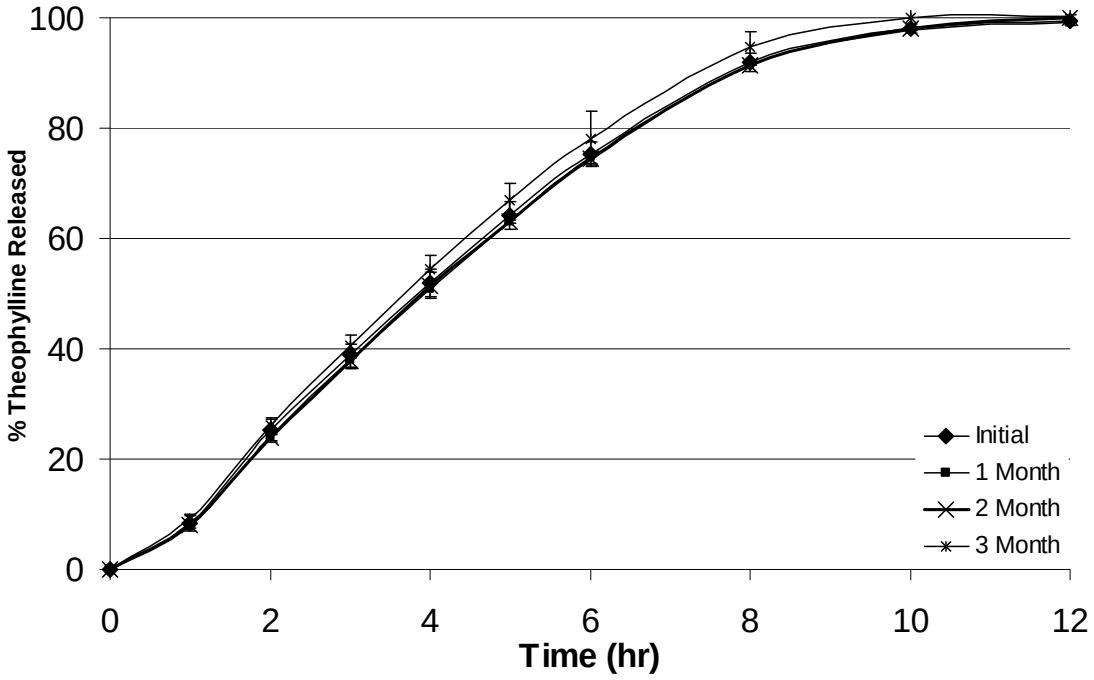


Figure 3.4 The influence of dispersion pH (2.5) on the release of theophylline from pellets coated with Eudragit® RS/RL 30 D (15% WG) containing 10% albumin and stored at 25°C/60% RH in hermetically sealed HDPE containers with desiccant (n=3). (Kucera, et al. *Drug Dev. Ind. Pharm.* Vol. 33 Issue 7 pp. 717-726)

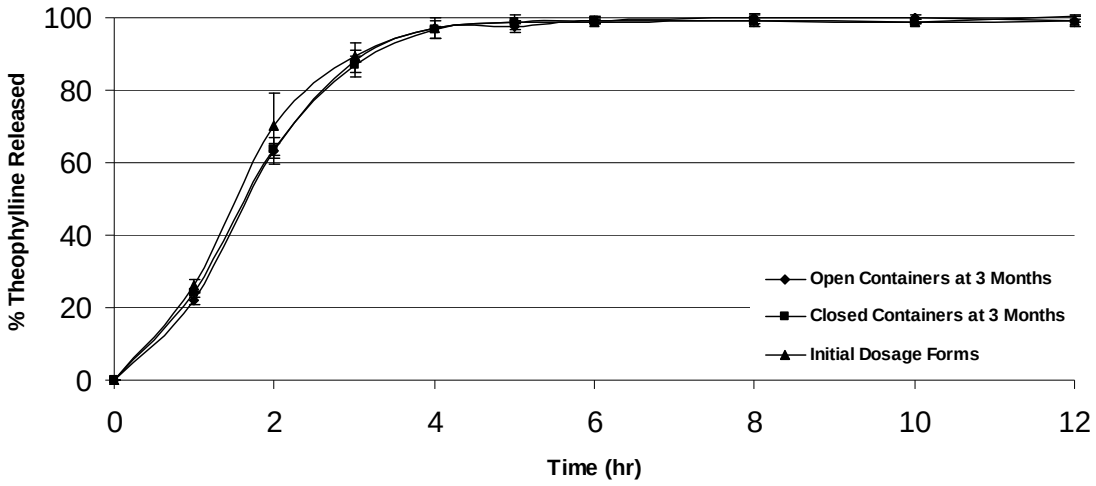


Figure 3.5 The effect of gelatin on the release of theophylline from pellets coated with Eudragit® RS/RL 30 D containing 10% gelatin and stored at 40°C/75% RH in open and closed containers (n=3). (Kucera, et al. *Drug Dev. Ind. Pharm.* Vol. 33 Issue 7 pp. 717-726)

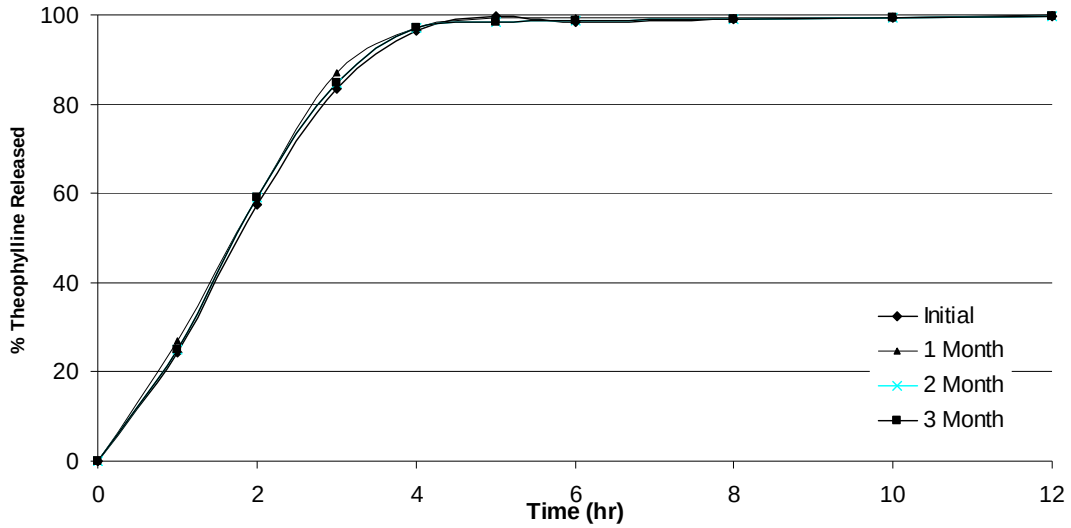


Figure 3.6 The influence of dispersion pH (2.5) on the release of theophylline from pellets coated with Eudragit® RS/RL 30 D (15% WG) containing 10% gelatin and stored at 40°C/75% RH in hermetically sealed HDPE containers with desiccant (n=3). (Kucera, et al. *Drug Dev. Ind. Pharm.* Vol. 33 Issue 7 pp. 717-726)

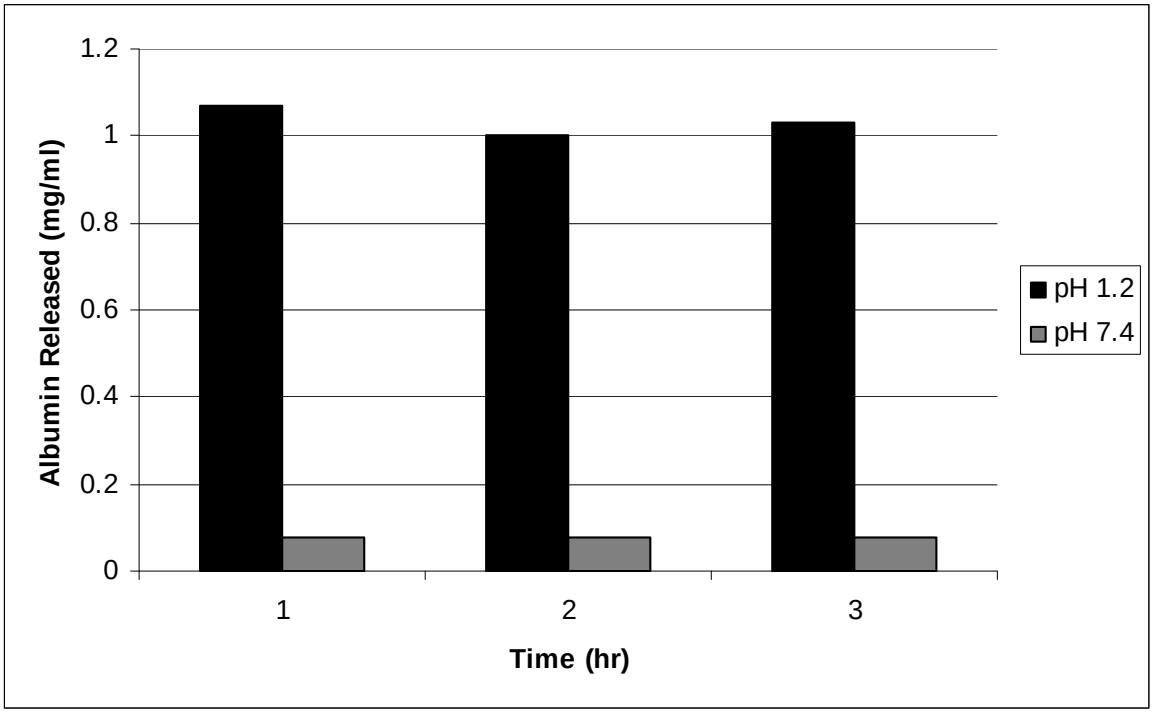


Figure 3.7 The effect of dissolution media pH on the release of albumin from Eudragit® RS/RL 30 D films plasticized with TEC (n=5). (Kucera, et al. *Drug Dev. Ind. Pharm.* Vol. 33 Issue 7 pp. 717-726)

Chapter 4: A Study on the Influence of Fumed Silicon Dioxide on the Stabilization of Eudragit® RS/RL 30 D Film-Coated Theophylline Pellets[3]

Abstract**:**

The objective of this study was to investigate the influence of various grades of fumed silicon dioxide on the drug release rate and physical aging of Eudragit® RS 30 D and RL 30 D coated theophylline pellets. Free films were assessed for both physico-mechanical properties and water vapor permeability with respect to time and storage conditions. The release rate of theophylline was influenced by the physical properties of the silicon dioxide employed. As the particle size of the silica dioxide decreased, there was an increase in dispersion viscosity, as well as a decrease in the theophylline release rate from the coated pellets. Films prepared from formulas containing Aeroperl® 300 had twice the water vapor transmission rate of films prepared from formulas containing Aerosil® 200 VV and Cab-O-Sil® M-5P and showed consistent moisture permeability values during storage for up to 1 month at 25°C/0% RH. SEM imaging of pellets coated with a formulation containing Aerosil® 200 VV or Cab-O-Sil® M-5P demonstrated film structures that were homogenous, while those coated with a formulation containing Aeroperl® 300 produced heterogeneous films with large particles of the excipient present within the polymeric matrix of the film. Stability in the drug release rate exhibited by pellets coated with a formulation containing Eudragit® RS 30 D, 15% TEC, and 30% Aeroperl® 300 was attributed to the stabilization of the moisture vapor transmission rate of the acrylic films. Increasing the concentration of Aeroperl® 300 in the coating formulation increased the theophylline release rate from coated pellets.

[3] Significant portions of this chapter were taken from: Kucera, S.A., D. Stimpel, N. Shah, A. Malick, M. Infeld, and J.W. McGinity. The Influence of Fumed Silicon Dioxide on the Stabilization of Eudragit® RS/RL 30 D Film-Coated Theophylline Pellets. *Pharm. Dev. Tech.* In Press. (2008)

4.1 INTRODUCTION

Film-coating with preparations of aqueous latex or pseudolatex dispersions has proven to be a popular method to manufacture sustained release dosage forms. The mechanism of film formation from colloidal aqueous systems is very complex, with surface tension and capillary effects being the driving force of coalescence between latex particles [1-4]. These forces are due to water evaporating from the system and result in the interdiffusion of polymer chains. A post-coat curing process, usually at temperatures above the glass transition temperature (T_g) of the polymer, is necessary to ensure that film formation is complete [5, 6]. Curing at temperatures that are too low or for an insufficient amount of time can result in products which are unstable due to continued coalescence of the latex particles during storage, resulting in a gradual decrease in drug release rates [1, 4, 7, 8]. As polymers undergo physical aging, there is a densification of the polymer which affects both the porosity and the tortuosity of the film [4, 9]. An increase in tortuosity coupled with a decrease in porosity will decrease the rate at which a drug permeates through the film. Being that all polymers used in sustained release applications undergo physical aging, the pharmaceutical scientist must select an appropriate stabilization system for that particular polymer. Previously, there have been several approaches to stabilize and prevent physical aging of film-coated dosage forms. These have included increasing the level of plasticizer in the film [1], utilizing high levels of talc [3], the addition of high T_g polymers [8, 10], the inclusion of immiscible polymers [4], and the addition of proteins [9].

An anti-adherent is a necessary component in a coating system to prevent sticking of the dosage forms during the manufacturing process. Talc is the most common anti-tack agent used in pharmaceutical applications and is usually present in concentrations of 25-100% based on the dry polymer weight, although a previous report has described processes in which 200% talc was employed [3]. Drawbacks to using such high

concentrations of talc include sedimentation in the feed lines and clogging of the nozzle during coating. Other researchers have reported that the use of glyceryl monostearate (GMS) at concentrations of 2-5% based on the dry polymer weight was sufficient as an anti-tack agent and was found to be superior to talc [11]. Colloidal silicon dioxide has also been used as an anti-tacking agent in film coating formulations [12]. Vecchio and coworkers reported that while there was a difference between the drug release rate from pellets coated with the very permeable Eudragit® RL 30 D and with a 80:20 blend of Eudragit® RL 30 D:Eudragit® RS 30 D when the formulation contained talc, no difference was found in the drug release rate between the two formulations when colloidal silicon dioxide was used. When the amount of colloidal silica in the formulation was increased, there was a decrease in the drug release rate, reported to be due to an increase in the thickness of a gel layer formed by the high amount of colloidal silicon dioxide present in the formulation. While the results of this investigation were interesting, no data were presented addressing the stability of the coated dosage forms.

In the present study, the influence of particle size of fumed silicon dioxide on the drug release rate and physical stability of theophylline pellets coated with Eudragit® RS 30 D and RL 30 D containing TEC as a plasticizer and either Cab-O-Sil® M-5P, Aerosil® 200 VV, or Aeroperl® 300 was investigated. It was hypothesized that the particles of colloidal silicon dioxide would act as a physical barrier to prevent the autoadhesion and further coalescence of the latex polymeric film during storage, resulting in acrylic-coated pellets that showed no change in drug release rate over time. The effect of silicon dioxide on both the mechanical properties and the permeability of cast films was also studied. The cross sectional morphology of coated pellets was investigated as well as the stability upon storage.

4.2 MATERIALS AND METHODS

4.2.1 Materials

Eudragit® RS 30 D and RL 30 D dispersions were donated by Degussa (Piscataway, NJ, USA). Triethyl citrate (TEC) was donated by Morflex, Inc. (Greensboro, NC, USA). Anhydrous theophylline and lactose monohydrate were both purchased from Spectrum Chemical (Gardena, CA, USA). Polyvinylpyrrolidone (Kollidon® K-30) was donated by the BASF Corp. (Mount Olive, NJ, USA). Microcrystalline cellulose (Avicel® PH-101) was donated by the FMC Corp. (Newark, DE, USA). Cab-O-Sil® M-5P was donated by the Cabot Corporation (Billerica, MA, USA). Aerosil® 200 VV and Aeroperl® 300 were both donated by the Degussa Corporation (Piscataway, NJ, USA). Imperial® 500 USP was generously donated by Luzenac America (Englewood, CO).

4.2.2 Methods

4.2.2.1 Preparation of Core Pellets

Anhydrous theophylline (25%), lactose monohydrate (45%) and microcrystalline cellulose (25%) were passed through a 30-mesh sieve and then mixed in a twin-shell blender for 15 minutes. A 12.5% w/v aqueous solution of polyvinylpyrrolidone (equivalent to 5% in the final formulation) was used as a binder in the wet-massing process. The wet mass was extruded using an LCI Benchtop Granulator (Tokyo, JP) at a rotation blade speed of 50 rpm. The extrudates were spheronized at 1000 rpm for 2 minutes using a Caleva Model 120 Spheronizer (Dorset, UK). The pellets were sieved after drying for 24 hours at 40°C, and the 16-20 mesh fraction was used for the coating trials.

4.2.2.2 Preparation of Coating Dispersions

Eudragit® RS 30 D and Eudragit® RL 30 D were combined with TEC (15%, based on the total dry polymer weight) and equilibrated with slow agitation via magnetic stir bar for two hours under ambient conditions. Silicon dioxide was dispersed in water over a period of two minutes using a POLYTRON homogenizer (Brinkmann Instruments, Westbury, NY, USA). The volume of the water was such that when the silica suspension was added to the acrylic dispersion, the coating formulation had total dispersed solids content of 15%. The aqueous silica dispersion was then added to the Eudragit® acrylic dispersion for a further 10 minutes of agitation via magnetic stir bar.

4.2.2.3 Film Coating

A 250-g batch of pellets containing 50% theophylline pellets and 50% 16-18 sugar spheres NF (Paulaur Corp., Cranbury, NJ, USA) was placed in a Strea-1 fluidized-bed coater (Aeromatic-Fielder, Bubendorf, SW). The sugar spheres were used to increase the volume of multi-particulates in the coating chamber during the process. The cores were preheated for 10 minutes at 40°C before the application of the coating dispersion. The dispersion was applied with a peristaltic pump through a 1.2 mm nozzle with an atomizing air pressure of 25 psi. The inlet temperature was 40-42°C and the outlet temperature was 32-35°C. To avoid pellet agglomeration, the dispersion was applied at a rate of 1 g/min until a theoretical weight gain of 2.5% had been reached and then increased to 3 g/min. The polymeric dispersion was stirred continuously throughout the coating process to prevent the sedimentation of dispersed solids. After coating, the pellets were dusted with 1.25 g of Imperial® 500 talc (0.5% based on the uncoated cores) and placed in a 40°C oven for 18 hours.

4.2.2.4 Stability Testing and In Vitro Drug Release

Coated pellets were placed in high density polyethylene containers which were hermetically sealed with aluminum induction seals with 1.0 g MINIPAX molecular sieve

(Impak Corporation, Los Angeles, CA) inside the container and then stored at 25°C/60% RH for up to 6 months. Dissolution testing was performed according to the United States Pharmacopeia (USP) 29 Apparatus II (Vankel VK 7000, Cary, NC, USA) over a 12-hour period in 900 ml of pH 7.4 (50 mM) phosphate buffer. The paddle speed was 50 rpm and the temperature of the media was maintained at 37±0.2°C.

300 mg of coated pellets (n=3) (containing 30 ± 3 mg API) were added to each dissolution vessel and 5-ml samples were removed by a Vankel 8000 Autosampler (Cary, NC, USA) after 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours. An infinity sample was obtained by mixing with a high-shear homogenizer (POLYTRON, Brinkmann Instruments, Westbury, NY, USA) for 1.5 minutes and the aqueous media was then analyzed for drug content. All dissolution tests were performed in triplicate.

The theophylline content of each sample was analyzed using ultraviolet (UV) spectroscopy. A volume of 150 µL was taken from each sample and placed in a corresponding well of a Falcon 96-well UV transparent plate (VWR International, West Chester, PA, USA). An equal volume of pH 7.4 dissolution media was added to each well to ensure that the concentrations were in the analytical range of the instrument. The tray was then loaded in to a μQuant 96-Well Plate Reader (Bio-Tek Instruments, Inc., Winooski, VT, USA) and analyzed for theophylline at a wavelength of 273 nm. The amount of theophylline released was calculated by taking the analyte concentration, comparing the value to the concentration of the infinity time point, and then multiplying by 100 to obtain a percentage of theophylline released at each time point.

4.2.2.5 Free Film Preparation

Films were prepared by using a casting method where either Eudragit® RS PO or Eudragit® RL PO was used in place of Eudragit® RS and RL 30 D, respectively. An amount of 30% silicon dioxide (based on the dry polymer weight) was placed in a volume of acetone (which would give the final dispersion a polymer/silicon dioxide content of 15%) and homogenized for two minutes with a POLYTRON (Brinkmann

Instruments, Westbury, NY, USA) high-shear mixer. TEC, at a concentration of 15% based on the dry polymer weight, was then added to the dispersion. The Eudragit® polymer was then added to the acetone dispersion and stirred with a magnetic bar for a period of 15 minutes. The resulting dispersion was separated into 50-ml fractions and cast into aluminum trays coated with BYTAC PTFE film (VWR International, Westchester, PA, USA). The films were allowed to dry for a period of 24 hour under ambient conditions and then placed in a 40°C oven for a further 48 hours to facilitate solvent removal. The films were allowed to equilibrate at 25°C/50% RH for 48 hours and then either tested for water vapor transmission rate or physico-mechanical properties, or stored at 25°C/0% RH for a period of up to 1 month to simulate pellet storage conditions.

4.2.2.6 Physico-Mechanical Testing

Stress-strain experiments with the cast films were performed using an Instron Model 4201 with a 1000 N load cell. Prior to testing, films were cut into 70 mm x 15 mm strips (n=5). The thickness was measured using a Mitutoyo Model ID-C1012EBS digital micrometer (Mitutoyo Corp., JP) and the average of five different measurements along the length of the film was determined. Stress-strain measurements were conducted on the cut films in accordance with ASTM guideline D 882-02 [13] using a gap distance of 50 mm, load range of 1 N and crosshead speed of 25 mm/min. The maximum tensile strength, percent elongation, and modulus of the films were calculated using Bluehill v.2.5 software.

4.2.2.7 Water Vapor Transmission Rate

The water vapor transmission rate of the cast films was determined according to guidelines set forth in ASTM E 96/E 96 – 05 [14] using the desiccant method. The thickness of each film was determined using a Mitutoyo Model ID-C1012EBS digital micrometer by measuring four points along the circumference and one point at the center

of a circular sample of film and averaging the values. The film sample was secured to the open mouth of an aluminum permeability cup (4 cm inner diameter and 3 cm depth) containing 20 g of Drierite® desiccant. The permeability cups (n=3) were accurately weighed, placed in a humidity chamber at 23°C/80% RH, and periodically reweighed over 96 hours to determine the weight gain. The water vapor transmission rate (WVT) and permeability (P) were calculated using the following equations:

$$WVT = (G/t)/A \qquad \text{(Eq. 4.1)}$$

$$P = \frac{WVT}{S} \times (R_1 - R_2) \times d \qquad \text{(Eq. 4.2)}$$

where G is the weight change, t is the time during which G occurred, A is the test area (cup mouth area), S is the saturation vapor pressure at test temperature, R_1 and R_2 are the relative humidity in the test chamber and inside the cup (0% RH for the desiccant method), respectively, and d is the thickness of the film.

4.2.2.8 Viscometry

Vecchio and associates [12] reported a decrease in drug release rate when the amount of silicon dioxide in a coating formulation was increased and attributed this to a thicker, more viscous gel silicon dioxide being present during dissolution. The viscosity of aqueous silicon dioxide dispersions was determined on fluids containing 6% w/w silicon dioxide. To make the dispersion, 12 g of silicon dioxide was dispersed in 200 ml of water for a period of two minutes using a POLYTRON (Brinkmann Instruments, Westbury, NY, USA) high-shear mixer. The dispersions were allowed to rest for five minutes and then the viscosity was measured using a Brookfield DV-I+ viscometer (Brookfield Engineering, USA) with an H1 spindle size at 30 ±1°C and 100 rpm (n=3).

4.2.2.9 Scanning Electron Microscopy

Scanning electron microscopy (SEM) was used to study the cross-sectional morphology of the polymeric films in coated pellets. The samples were mounted on an aluminum stage using carbon tape and coated for 45 seconds with gold-palladium in an argon environment using a Pelco® Model 3 Sputter Coater (Ted Pella, Inc., Redding, CA). Examination of the samples was carried out using a Hitachi S-4500 field emission microscope operating at an accelerating voltage of 5 kV. Images were captured with Quartz® PCI software (Quartz Imaging Corporation, Vancouver, B.C. Canada).

4.2.2.10 Statistical Treatments

Statistical analysis of *in vitro* dissolution data was measured using the f_2 similarity factor treatment described by Shah and associates [15]. To ensure that a bias in the f_2 similarity factor was not increased, only time points below 85% dissolution were utilized. MINITAB® Release 14 was used for the statistical analysis of the physico-mechanical properties and water vapor permeability of films using a one-way ANOVA with Tukey's HSD test, $\alpha = 0.05$.

4.3 RESULTS AND DISCUSSION

At the glass transition temperature of the polymer, the molecules are effectively locked in position in the polymeric glass, yet are free to rotate and translate until the lowest possible energy configuration is achieved [16]. These movements in the polymeric film result in a decrease in void volume of the film [1, 4-6], influencing both the tortuosity and the porosity. These changes are often reflected by a decrease in the water vapor transmission rate of free films [4]. The water vapor permeability of cast films are shown in Figure 4.1. A sample size of three films was tested initially after manufacturing, with the remaining films stored at 25°C/0% RH and tested after 1 week and after 1 month. A comparison of the initial results showed that acrylic films containing Cab-O-Sil® M5P and Aerosil® 200 VV Pharma yielded similar permeabilities;

while the formulation containing the larger particle size of silicon dioxide (Aeroperl® 300) had water vapor permeability values that were double those of the colloidal grade at the same time point. Similar results were also reported by Okhamafe and York when investigating the permeability of hypromellose films containing talc and titanium dioxide [17]. They found a decrease in diffusion of water through the cellulosic membrane as the particle size of the additives decreased and the surface area of the insoluble excipients were increased. Cast acrylic films containing 30% Aeroperl® 300 were found to exhibit stable water vapor transmission when stored for 1 month at 25°C/0% RH, while films containing Cab-O-Sil® M-5P and Aerosil® 200 VV exhibited decreases and increases, respectively, in this parameter.

The physico-mechanical properties of films have been used to investigate the physical aging of polymers. Densification of a polymeric film will result in an increase in both the elastic modulus and tensile strength and a decrease in the elongation of polymeric films. The physico-mechanical properties of these films are reported in Table 4.1. Although those films containing Aeroperl® 300 showed no difference in modulus or tensile strength, there was a significant decrease in elongation, indicating physical aging in these systems. Those films containing Cab-O-Sil® M-5P showed no increase in either maximum tensile strength or modulus. Films that employed Aerosil® 200 VV exhibited a statistical increase in maximum tensile strength which could indicate physical aging in these systems. When comparing the tensile strength of the films of the three different formulations, this parameter was found to be significantly lower for the formulation employing Aeroperl® 300. Incorporation of the particles in the film can cause discontinuities in the network of the polymer matrix, resulting in a weak link in the structure of the film [18]. Thus, the presence of the large agglomerates of silicon dioxide in the films caused areas of shear stress which, in turn, affected the tensile strength of the film. The films used to determine both the water vapor permeability and physico-mechanical properties were manufactured via a solvent evaporation process, as opposed

to the films formed from the aqueous lattices used during the coating of multi-particulates. Care should be taken when attempting to extrapolate results from films formed by two different processes; however, it has been previously reported that films created from both aqueous and solvent methods aged in similar fashions when the physico-mechanical properties of said films were investigated [19].

The viscosity of silicon dioxide dispersion was found to depend upon the bulk density and secondary particle size of the silicon dioxide grade as seen in Figure 4.2. Cab-O-Sil® M-5P and Aerosil® 200 VV differ primarily in particle size and bulk density. While both grades have the same primary aggregate size of 150-300 nm, Aerosil® 200 VV is mechanically compacted, giving it a larger secondary agglomerate size that only very high shear forces can break. When comparing the two grades of silicon dioxide with particle sizes in the colloidal range, Cab-O-Sil® M-5P produced dispersions of the highest viscosity and also possessed the lowest bulk density value of 40 g/L, while Aerosil® 200 VV possessed a lower viscosity and higher bulk density of 120 g/L. These values indicate that the high shear forces imparted on the Aerosil® 200 VV when being dispersed in water were insufficient to break up the secondary agglomerates. The granulated grade of silicon dioxide, Aeroperl® 300, had the lowest viscosity values and also the highest particle size (30 μm) and bulk density (280 g/L).

Pellets were coated with a blend of Eudragit® RS 30 D: RL 30 D (95:5), 15% TEC as a plasticizer, and 30% silicon dioxide to a weight gain of 10% based on the dry polymer to investigate the influence of silicon dioxide on stabilizing the drug release rate from coated dosage forms after storage. It was found that the grade of silicon dioxide used as a glidant in the coating formulation greatly influenced the theophylline release rate from coated pellets, as shown in Figure 4.3. The drug release rate was proportional to the particle size and bulk density of the grade of silicon dioxide used in the coating formulation. It was hypothesized that the decrease in drug release rate seen with the colloidal grades of silicon dioxide was due to viscous gel formation during dissolution

[12]. The cross-sectional morphology of coated pellets (Figure 4.4) demonstrated that the Aeroperl® 300 was still present as large agglomerates in the film coating surrounding the pellet. These large agglomerates produced films of high permeability, as was confirmed in the water vapor permeability results reported in Figure 4.1. Although not reflected in the water vapor permeability studies, pellets coated with the formulation containing Aerosil® 200 VV demonstrated a faster drug release rate than those coated with the formulation containing Cab-O-Sil® M-5P. The cross-sectional morphology of the pellets showed that both grades produced dense, coherent film coatings with the coating containing Aerosil® 200 VV showing striations which would be indicative of the denser material present in its compacted form. While there was a significant difference in the drug release profile between formulations using these two excipients, the variation between the permeability of films employing these two excipients during water vapor transmission studies was negligible. During dissolution, the excipient is in intimate contact with water in the dissolution fluid, allowing for the hydration of the silicon dioxide which eases the diffusion of drug from the core. The method used to measure the water vapor permeability of the films does not take into account the hydrophobicity of the polymer used in the film coating, explaining why films of different formulations could exhibit a permeability of the same magnitude, while pellets coated with the same formulations demonstrate dissimilar *in vitro* drug dissolution rates.

Coated theophylline pellets that released ≥80% API after 12 hours were desired for a sustained release model system. Optimization of the drug release rate was performed for pellets coated with the formulations containing Aerosil® 200 VV, Cab-O-Sil® M-5P, and Aeroperl® 300 (Table 4.2). A blend of 90:10, Eudragit® RS 30 D: RL 30 D, and 15% TEC offered drug release profiles that fit the requirements of the sustained release model system for formulations which contained 30% Cab-O-Sil® M-5P (Figure 4.5) or Aerosil® 200 VV (Figure 4.6). Increasing the fraction of highly permeable Eudragit® RL 30 D to 10%, compared to 5%, increased the drug release rate so that

between 85 and 90% of the drug was released after 12 hours when a weight gain of 15% (based on the dry polymer weight) was applied to the theophylline pellets. The increase in release rate of theophylline from the formulation containing Aeroperl® 300 was mitigated by applying a 20% weight gain (based on the dry polymer weight) of poorly permeable Eudragit® RS 30 D with 15% TEC as a plasticizer (Figure 4.7).

The coated pellets were stored in aluminum-induction sealed HDPE containers with desiccant at 25°C/60%RH. The effect of storage for pellets coated with the formulation containing Cab-O-Sil® M-5P is depicted in Figure 4.5. There was a small decrease in the drug release rate during storage of these dosage forms over time, which is consistent with the results from the water vapor permeability studies that demonstrated a decrease in the water vapor permeability during storage after 1 month at the same conditions (Figure 4.1). When statistical analysis of dissolution data was performed between pellets after curing and those stored for 6 months, the f_2 factor in the test for similarity was 64, indicating a slightly greater than 5% average change in theophylline release rate during storage (f_2=65 indicates a 5% change). The addition of 30% Aerosil® 200 VV had the opposite effect on the stability of the drug release rate during storage. When stored at the same conditions for 6 months (Figure 4.6), there was an increase in drug release rate, which correlates to the increase in water vapor transmission rate of cast films discussed earlier. The f_2 similarity factor between the initial and 6 month sample was 62, representing an increase of slightly greater than 5% in the average drug release rate. In contrast, the addition of 30% Aeroperl® 300 to the coating formulation was sufficient to stabilize the drug release rate from film-coated theophylline pellets during storage for 2 moths at 25°C/60% RH (Figure 4.7). Dissolution profiles were super-imposable over one another at 2 months, and an f_2 value of 92 denoted an average variation of less than 2%. Stabilization in the drug release rate from these coated pellets can be explained by the water vapor permeability results, which showed no change in this parameter during storage over one month at 25°C.

Vechhio and coworkers found that replacing talc with 30% colloidal silicon dioxide in the coating formulation increased the drug release rate when compared to pellets coated with an identical formulation in which 30% talc was used [12]. The authors also found that increasing the concentration of silicon dioxide from 30% to 60% decreased the drug release rate, presumably due to the formation of an increased gel layer which would serve to delay the release of drug from the coated dosage form. In our studies, it was found that as the concentration of Aeroperl® in the coating formulation was increased, there was an increase in the drug release rate (Figure 4.8). These results can be explained by examining the cross-sectional morphology of coated pellets as seen in Figure 4.4. As the fraction of insoluble excipient was increased in the coating formulation, the coalescence of the acrylic polymer became interrupted by the presence of the large agglomerates of silicon dioxide. The acrylic polymer functioned as a binding agent for the silicon dioxide, resulting in incomplete film formation and producing a film that became hydrated very quickly upon intimate contact with dissolution media. This decrease in tortuosity of the film coating resulted in an increase in the theophylline release rate from coated pellets. Maejima and coworkers showed the opposite effect when examining the influence of talc concentration on the stability and drug release rate of Eudragit® RS/RL 30 D coated theophylline pellets. As the concentration of talc was increased from 50% to 100% (based on the dry polymer weight), there was a decrease in the permeability coefficient of the films and the polymeric weight gain needed to equalize the drug release rate was decreased for the higher level of talc [3]. These researchers found that although the acrylic polymer functioned as a binding agent for the talc, increasing concentrations of the hydrophobic excipient functioned to sustain the release of the drug during dissolution. The effect of increasing the concentration of silicon dioxide was contrary to that of increasing talc concentration due to the large particle size and hydrophilicity of Aeroperl® 300 which increased membrane permeability and the hydrophobic nature of talc, which formed less permeable films.

4.4 CONCLUSIONS

The rate of drug release was influenced by the grade of silicon dioxide used in the coating formulation. Excipients with a particles size in the colloidal range resulted in dosage forms that showed a slower drug release profile, due to an enhanced incorporation of the smaller particle size silicon dioxide in the polymeric matrix of the film. Increasing the concentration of Aeroperl® 300 in the coating formulation interrupted the coalescence of the acrylic polymers, creating films that were more permeable and final products that showed faster drug release rates. Increases and decreases in drug release rate from theophylline pellets coated with acrylic dispersions containing Aerosil® 200 VV and Cab-O-Sil® M-5P, respectively, were due to instabilities in the water vapor permeability of these films; however, the difference in the drug release rate between the initial and 6-month samples was about 5%. The addition of 30% Aeroperl® 300 to Eudragit® RS 30 D films plasticized with 15% TEC stabilized theophylline release profiles, with no significant change in the release rate for pellets stored at 25°C and 60% relative humidity in aluminum induction sealed HDPE containers. The stabilization in drug release was attributed to the permeability parameter of the acrylic film.

4.5 REFERENCES

1. Amighi, K. and A.J. Moës. Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit® RS 30 D film-coated sustained-release theophylline pellets. European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42** (1): p. 29-35.

2. Lippold, B.C. and R.M. Pages. Film Formation, Reproducibility of Production and Curing with Respect to Release Stability of Functional Coatings from Aqueous Polymer Dispersions. Pharmazie, 2001. **56** (1): p. 5-17.

3. Maejima, T. and J.W. McGinity. Influence of Film Additives on Stabilizing Drug Release Rates from Pellets Coated with Acrylic Polymers. Pharm. Dev. Tech., 2001. **6** (2): p. 211-221.

4. Zheng, W., D. Sauer and J.W. McGinity. Influence of hydroxyethylcellulose on the drug release properties of theophylline pellets coated with Eudragit® RS 30 D. European Journal of Pharmaceutics and Biopharmaceutics, 2005. **59** (1): p. 147-154.

5. Frisbee, S.E., K.A. Mehta and J.W. McGinity. Processing Factors that Influence the In Vitro and Performance of Film-Coated Drug Delivery Systems. Drug Delivery Technology, 2002. **21** (1): p. 72-76.

6. Wu, C. and J.W. McGinity. Influence of methylparaben as a solid-state plasticizer on the physicochemical properties of Eudragit(R) RS PO hot-melt extrudates. European Journal of Pharmaceutics and Biopharmaceutics, 2003. **56** (1): p. 95-100.

7. Amighi, K. and A.J. Moës. Influence of curing conditions on the drug release rate from Eudragit NE 30 D film coated sustained-release theophylline pellets. S.T.P. Pharma Sci, 1997. **7** (2): p. 141-147.

8. Wu, C. and J.W. McGinity. Influence of an Enteric Polymer on Drug Release Rates of Theophylline from Pellets Coated with Eudragit RS 30 D. Pharm. Dev. Tech., 2003. **8** (1): p. 103-110.

9. Kucera, S.A., N.H. Shah, A.W. Malick, M.A. Infeld and J.W. McGinity. The Use of Proteins to Minimize the Physical Aging of Eudragit® Sustained Release Films. Drug Development and Industrial Pharmacy, 2007. **33** (7): p. 717-726.

10. Zheng, W. and J.W. McGinity. Influence of Eudragit® NE 30 D Blended with Eudragit® L 30 D-55 on the Release of Phenylpropanolamine Hydrochloride from Coated Pellets. Drug Development and Industrial Pharmacy, 2003. **29** (3): p. 357-366.

11. Petereit, H.U., M. Assmus and K. Lehmann. Glyceryl monostearate as a glidant in aqueous film-coating formulations. European Journal of Pharmaceutics and Biopharmaceutics, 1995. **41** (4): p. 219-228.

12. Vecchio, C., F. Fabiani and A. Gazzaniga. Use of Colloidal Silica as a Separating Agent in Film Forming Processes Performed with Aqueous Dispersion of Acrylic Resins. Drug Development and Industrial Pharmacy, 1995. **21** (15): p. 1781-1787.

13. ASTM. ASTM D 882-02: Standard Test Method for Tensile Properties of Thin Plastic Sheeting. 2002.

14. ASTM. ASTM E 96/E 96 M-05: Standard Test Methods for Water Vapor Transmission of Materials. 2005.

15. Shah, V.P., Yi Tsong, Pradeep Sathe, and Jen-Pei Liu. *In Vitro* Dissolution Profile Comparison - Statistics and Analysis of the Similariry Factor, f_2. Pharmaceutical Research, 1998. **15** (6): p. 889-896.

16. Guo, J.-H. Aging processes in pharmaceutical polymers. Pharm. Sci. Technol. Today, 1999. **2** (12): p. 478-483.

17. Okhamafe, A.O. and P. York. Effect of solids-polymer interactions on the properties of some aqueous-based tablet film coating formulations. II. Mechanical characteristics. International Journal of Pharmaceutics, 1984. **22** p. 273-281.

18. Okhamafe, A.O. and P. York. Relationship between stress, interaction and the mechanical properties of some pigmented tablet coating films. Drug Development and Industrial Pharmacy, 1985. **11** (1): p. 131-146.

19. Gutierrez-Rocca, J.C. and J.W. McGinity. Influence of Physical Aging on the Physical-Mechanical Properties of Acrylic Resin Films Cast from Aqueous Dispersions and Organic Solutions. Drug Dev. Ind. Pharm., 1993. **19** (3): p. 315-332.

4.6 TABLES

Modulus (MPa)

	Initial	1 Week	1 Month
Cab-O-Sil® M-5P	143.64 ± 10.43	138.60 ± 5.36	127.75 ± 9.01
Aerosil® 200 VV	136.92 ± 5.29	133.87 ± 6.20	136.45 ± 4.64
Aeroperl® 300	147.11 ± 6.14	143.48 ± 7.56	139.89 ± 11.13

Elongation at Break (%)

	Initial	1 Week	1 Month
Cab-O-Sil® M-5P	26.08 ± 5.84	31.89 ± 10.28	35.19 ± 5.74
Aerosil® 200 VV	28.10 ± 6.21	26.84 ± 1.22	30.55 ± 3.61
Aeroperl® 300	26.40 ± 6.75	36.36 ± 5.44	16.68 ± 1.07

Tensile Strength at Max Load (MPa)

	Initial	1 Week	1 Month
Cab-O-Sil® M-5P	8.74 ± 0.21	9.37 ± 0.19	8.85 ± 0.34
Aerosil® 200 VV	8.90 ± 0.47	10.04 ± 0.27	9.85 ± 0.04
Aeroperl® 300	3.12 ± 0.38	2.77 ± 0.17	2.83 ± 0.21

Table 4.1 The influence of time and temperature on the physico-mechanical properties of films containing 90:10 Eudragit® RS 30 D:RL 30 D, 15% TEC, and either Cab-O-Sil® M-5P or Aerosil® 200 VV or Eudragit® RS 30 D, 15% TEC, and Aeroperl® 300 (n=5). (In Press, *Pharmaceutical Development and Technology*)

	Formulation				
Excipient	1	2	3	4	5
Eudragit® RS 30 D (g)	123.75	123.75	183.33	183.33	183.33
Eudragit® RL 30 D (g)	13.75	13.75	-	-	-
TEC (g)	6.19	6.19	8.25	8.25	8.25
Cab-O-Sil® M-5P (g)	12.38	-	-	-	-
Aerosil® 200 VV (g)	-	12.38	-	-	-
Aeroperl® 300 (g)	-	-	16.50	27.50	55.00

Table 4.2 Composition of polymeric dispersions used in coating experiments (all diluted with water to 15% solids and adjusted for a 10% overage). (In Press, *Pharmaceutical Development and Technology*)

4.7 FIGURES

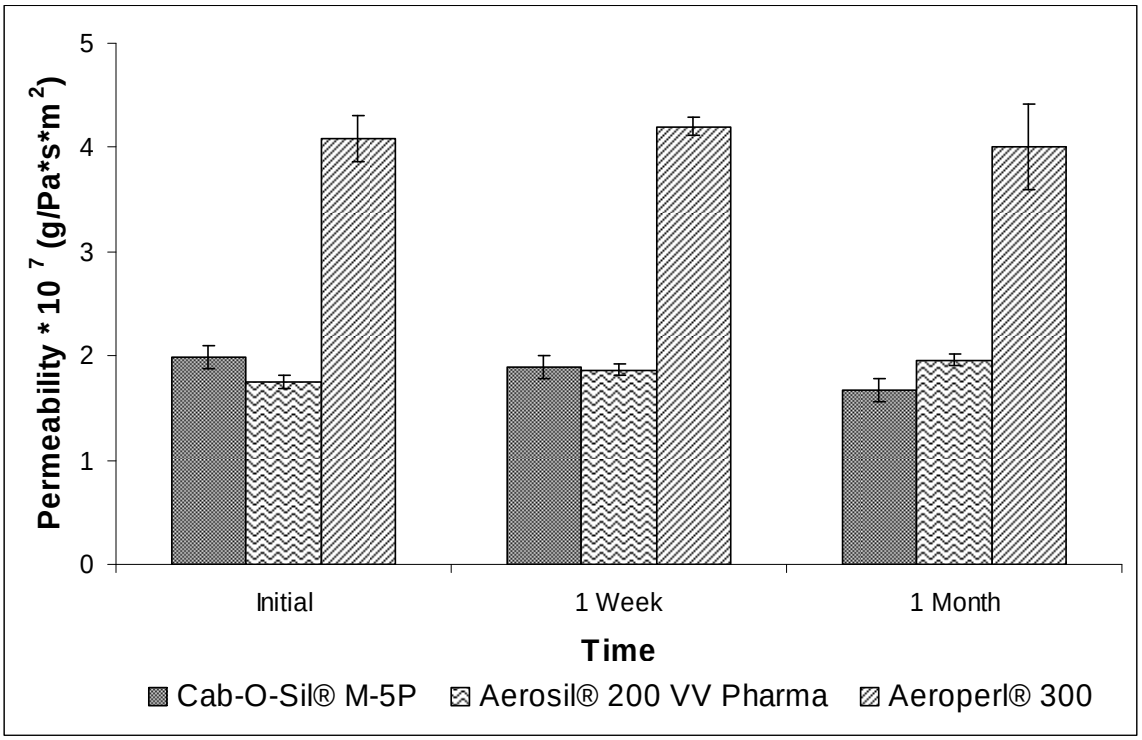


Figure 4.1 The effect of temperature and time on the water vapor permeability of cast films containing Eudragit® RS/RL 30D, 15% TEC and 30% silicon dioxide (25°C/80% RH, n=3). (In Press, *Pharmaceutical Development and Technology*)

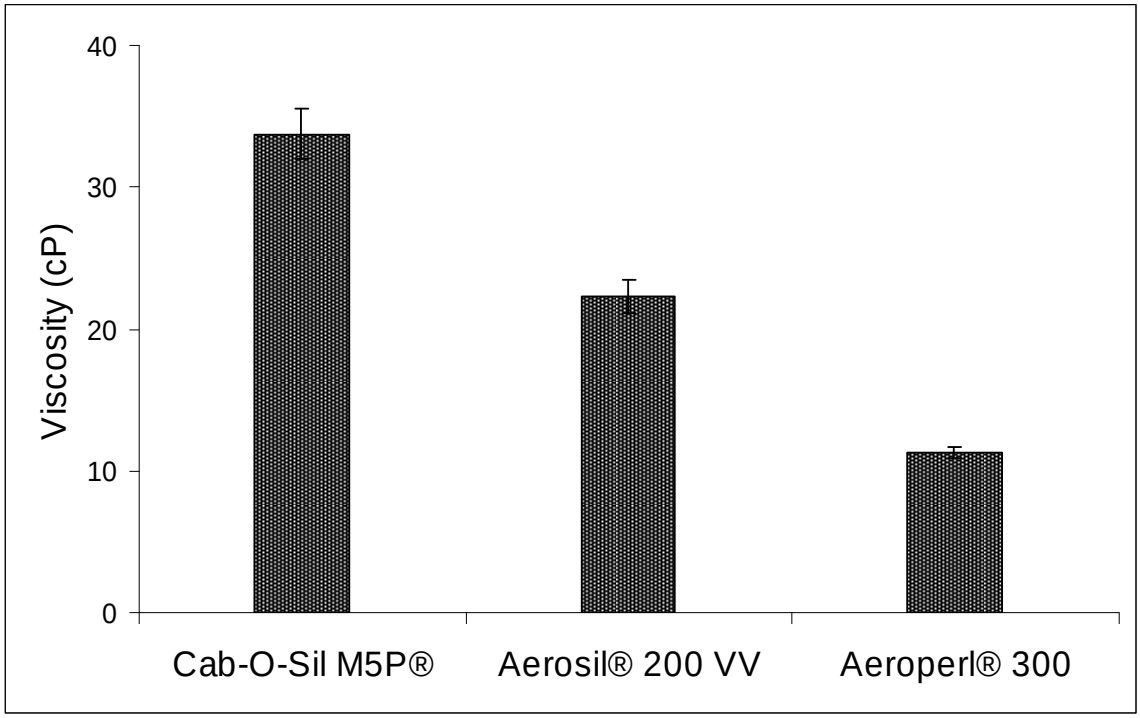


Figure 4.2 The effect of silicon dioxide type on the viscosity of a 6% aqueous dispersion at 30°C (n=3). (In Press, *Pharmaceutical Development and Technology*)

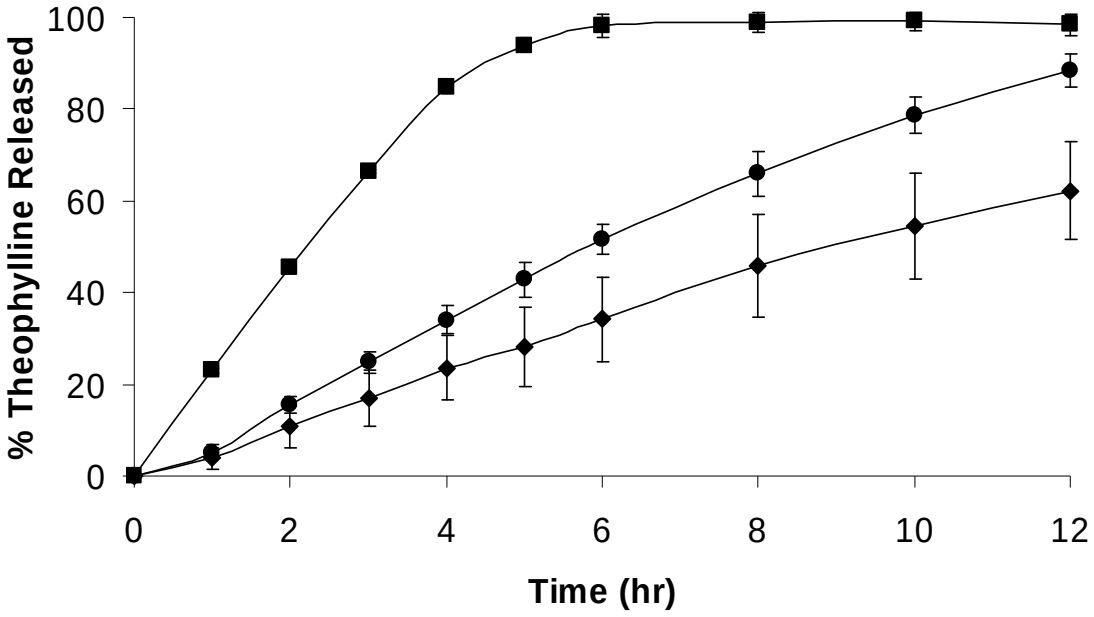


Figure 4.3 The influence of silicon dioxide type on the release of theophylline (30 mg) from pellets coated with Eudragit® RS 30 D:RL 30 D (95:5), 15% TEC, and 30% silicon dioxide (■ - Aeroperl® 300, ● - Aerosil® 200 VV, ◆ - Cab-O-Sil® M-5P) (USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, n=3). (In Press, Pharmaceutical Development and Technology)

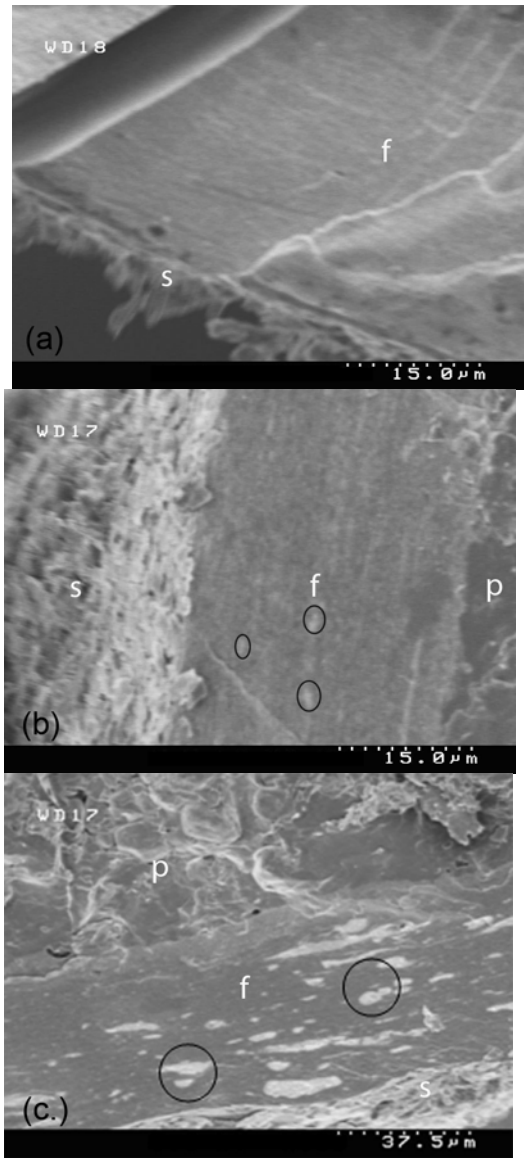


Figure 4.4 Scanning electron microscope cross-sections of pellets coated with silicon dioxide-containing formulations plasticized with TEC (a.) Eudragit® RS:RL 30 D (90:10), 15% TEC, 30% Cab-O-Sil® M-5P; (b.) Eudragit® RS:RL 30 D (90:10), 15% TEC, 30% Aerosil® 200 VV Pharma; (c.) Eudragit® RS 30 D, 15% TEC, 30% Aeroperl® 300 (s=surface, f=film, p=pellet). (In Press, *Pharmaceutical Development and Technology*)

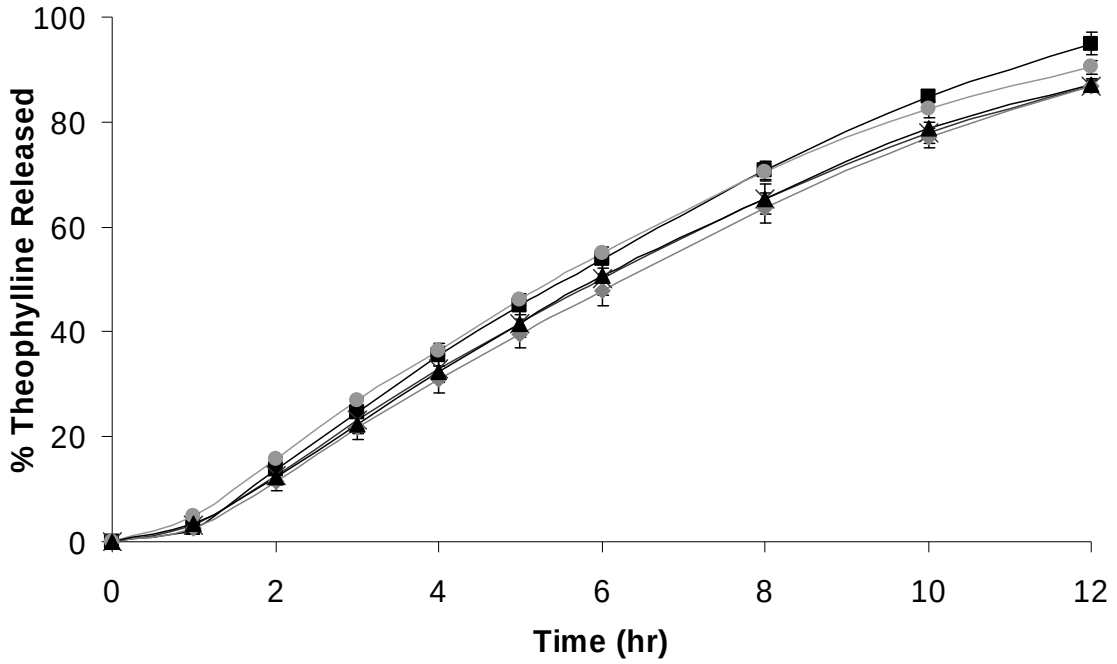


Figure 4.5 The influence of storage time on the release of theophylline (30 mg) from pellets coated with Eudrgit® RS/RL 30 D (90:10) containing 30% Cab-O-Sil® M-5P and 15% TEC (Formulation 1) coated to a 15% weight gain and stored in sealed HDPE containers with desiccant at 25°C/60% (■ - Initial, × - 1 Month, ◆ - 2 Month, ● - 3 Month, ▲ - 6 Month) (USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, n=3). (In Press, *Pharmaceutical Development and Technology*)

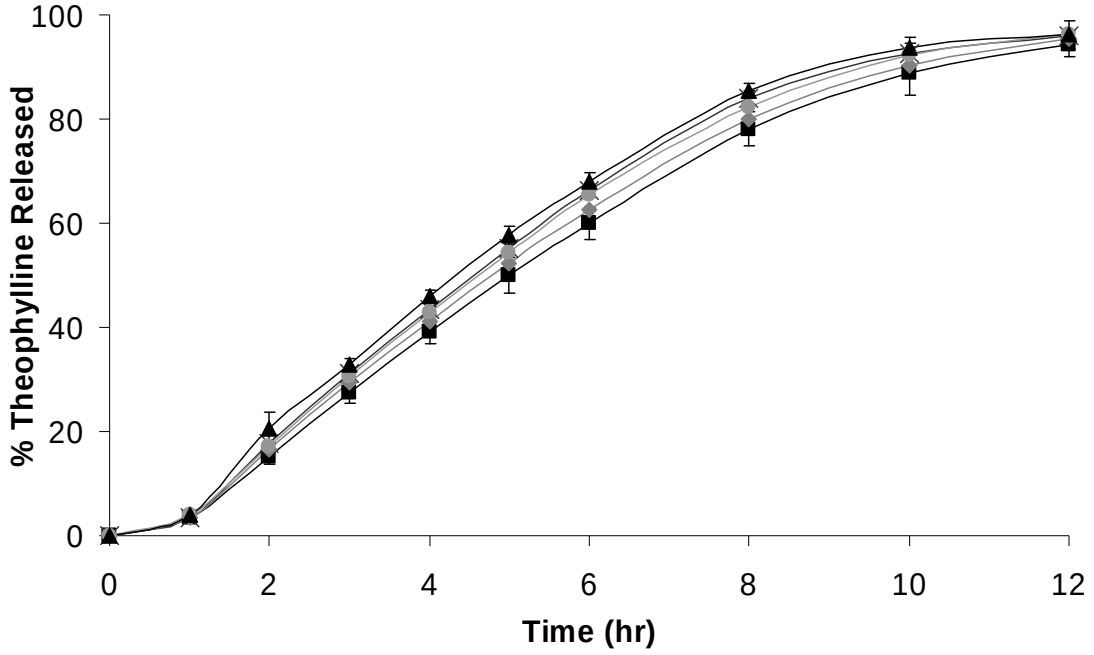


Figure 4.6 The influence of storage time on the release of theophylline (30 mg) from pellets coated with Eudragit® RS/RL 30 D (90:10) containing 30% Aerosil® 200 VV Pharma, 15% TEC (Formulation 2) and coated to a 15% weight gain and stored in sealed HDPE containers with desiccant at 25°C/60% RH (■ - Initial, × - 1 Month, ◆ - 2 Month, ✹ - 3 Month, ▲ - 6 Month) (USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, n=3). (In Press, *Pharmaceutical Development and Technology*)

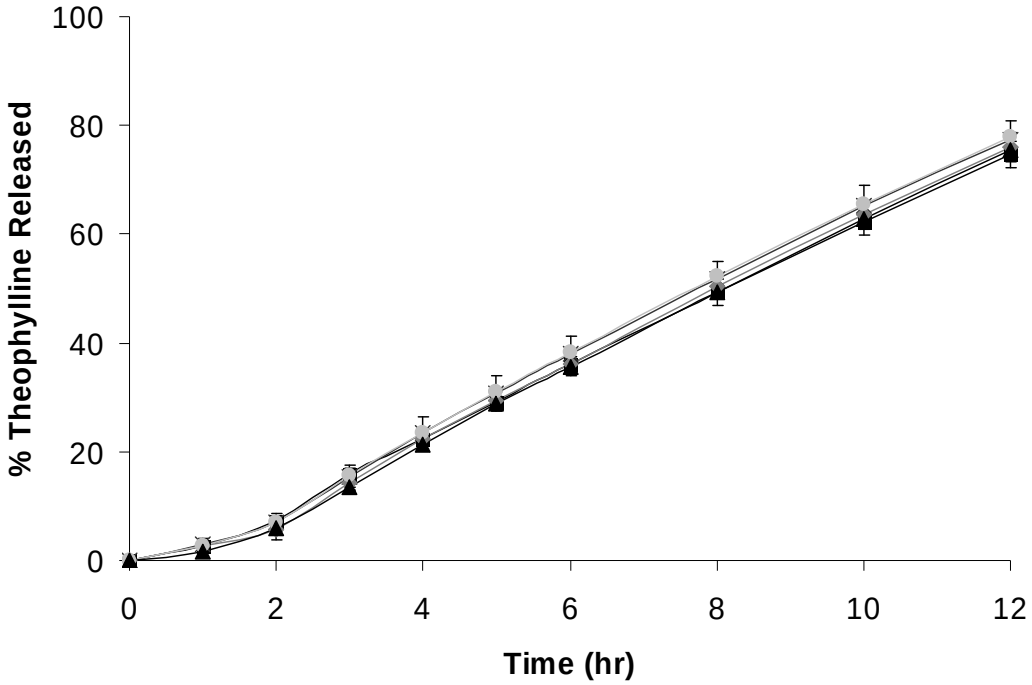


Figure 4.7 The influence of storage time on the release of theophylline (30 mg) from pellets coated with Eudragit® RS 30 D containing 30% Aeroperl® 300, 15% TEC (Formulation 3) and coated to a 20% weight gain and stored in sealed HDPE containers with desiccant at 25°C/60% RH (■ - Initial, × - 1 Week, ◆ - 2 Week, ✹ - 1 Month, ▲ - 2 Month) (USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, n=3). (In Press, *Pharmaceutical Development and Technology*)

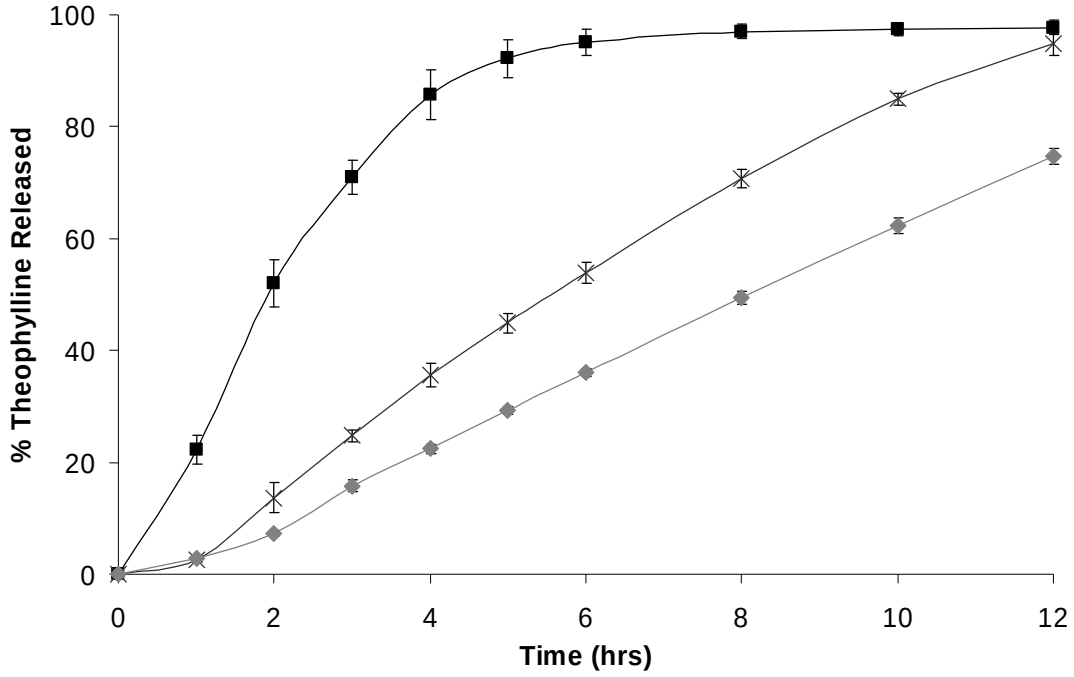


Figure 4.8 Influence of Aeroperl® 300 concentration (based on dry polymer weight) on the release of theophylline from pellets coated (20% WG) with Eudragit® RS 30 D and 15% TEC (■ - 100% (Formulation 5), × - 50% (Formulation 4), ◆ - 30% (Formulation 3)) (USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, n=3). (In Press, *Pharmaceutical Development and Technology*)

Chapter 5: An Investigation of the Influence of Ethylcellulose Polymers on the Physical Stability of Theophylline Pellets Coated with Eudragit® NE 30 D[4]

Abstract:

The objective of this study was to investigate the influence of ethylcellulose (EC), a high glass transition temperature, non-enteric polymer, on the physical stability and drug release properties of theophylline from pellets coated with the poorly permeable, pH-independent, sustained release coating dispersion, Eudragit® NE 30 D. The effect of EC addition on drug release from coated pellets, as well as the physico-mechanical, water vapor permeability, and thermal properties of sprayed films was investigated. The particle size of EC, when mixed in a ratio of 1:1 with the acrylic polymer, affected the drug release rate, with those formulations possessing a smaller particle size exhibiting increased drug release rates. When EC having a mean particle size of 9 μm was present in the acrylic films at a ratio of 1:2, 60% drug was released over 18 hours. The drug release rate from these coated theophylline pellets was stable over 3 months at both 25°C/60% RH and 40°C/75% RH when stored in aluminum induction sealed, high density polyethylene (HDPE) containers. Sprayed films stored under the same conditions showed no change in the water vapor permeability and physico-mechanical properties. Modulated differential scanning calorimetry showed 3 transitions in the composite films, corresponding to the glass transition temperature of Eudragit® NE 30 D, ethylcellulose, and a third miscible phase. This third miscible phase was determined to consist of 85%

[4] Significant portions of this chapter were taken from: Kucera, S.A., C. Tessmann, N. Shah, A. Malick, M. Infeld, and J.W. McGinity. The Influence of Ethylcellulose Polymers on the Physical Stability of Theophylline Pellets Coated with Eudragit® NE 30 D. This paper is under review by the *Journal of Drug Delivery Science and Technology*.

ethylcellulose and 15% acrylic polymer and occupied only a small fraction of the total film.

5.1 INTRODUCTION

The application of aqueous dispersions to solid oral dosage forms is one of the most common approaches to achieve sustained drug release in the body. The number of aqueous systems available for this application, however, is quite limited and all polymers used in sustained release applications have shown physical instabilities during storage [1-3]. These instabilities can result in either an increase or decrease in the drug release rate over time as a function of both temperature and relative humidity.

Eudragit® NE 30 D is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate with neutral ester functionality and has previously been used as both a granulating agent [4-9] and a modified release film coating agent [10-14]. The films formed from these dispersions are insoluble, poorly permeable, and exhibit pH-independent swelling during dissolution testing. The polymer requires no additional plasticization due to its low Tg and forms films that are highly flexible with good compression properties. When sprayed onto solid oral dosage forms, this material forms a physical barrier to drug diffusion and the rate of drug release is controlled by the thickness of the membrane, with thicker films resulting in slower drug release rates.

There have been reports in the scientific literature, however, of instabilities in drug release for dosage forms coated with this Eudragit® NE 30 D [2, 14]. Formulating with Eudragit® NE 30 D is further complicated by the fact that solid oral dosage forms can exhibit both increases and decreases in drug release rate as a function of time and storage conditions. Decreases in drug release rate are seen during the initial swelling of the polymer and are due to the further gradual coalescence of the material during storage,

while increases in drug dissolution rate are due to the presence of endogenous excipient utilized in the preparation of the dispersion [15]. The polymeric dispersion is manufactured via emulsion polymerization with the use of nonoxynol 100 as a surfactant. Nonoxynol 100 has a relatively high melting point of about 65°C, which has been shown to crystallize in the films during storage at low temperatures [15, 16]. These crystals are water soluble and dissolve quickly during dissolution testing, forming pores in the coating and leading to faster drug release from aged samples.

There is a paucity of research reported in the literature on stabilizing film-coated dosage forms employing Eudragit® NE 30 D. Recently, the addition of a miscible, high T_g enteric polymer (Eudragit® L 30 D-55) to Eudragit® NE 30 D was shown to decrease the sticking of multi-particulate dosage forms during both coating and subsequent storage at elevated temperatures [14]. Over time, pellets coated with a blend of these two polymers also showed stable drug release rates in 0.1 N HCl after curing for 4 hours at 60°C. However, more research in stabilizing this sustained release polymer is needed.

The objective of the present study was to investigate the effect of a high T_g non-enteric polymer, Ethocel®, on the drug release rate and physical stability of theophylline pellets coated with Eudragit® NE 30 D. It was hypothesized that the substantially immiscible, EC polymer would function to decrease the degree of coalescence of the acrylic polymer and stabilize the drug release rate of coated multi-particulates over time when stored at both ambient and accelerated conditions. The effect of ethylcellulose particle size and molecular weight on the drug release rate of coated pellets was investigated. The influence of fine particle ethylcellulose on the stabilization of drug release rates of coated pellets, the physico-mechanical properties, and the water vapor permeability of free films was also studied.

5.2 MATERIALS AND METHODS

5.2.1 Materials

Eudragit® NE 30 D dispersions were donated by Degussa, Röhm America (Piscataway, NJ, USA). Ethocel® S4 and S7 FP cellulosic polymers were donated by Colorcon (West Point, PA, USA). Anhydrous theophylline and lactose monohydrate were both purchased from Spectrum Chemical (Gardena, CA, USA). Polyvinylpyrrolidone (Kollidon® K-30) was donated by the BASF Corp. (Mount Olive, NJ, USA). Microcrystalline cellulose (Avicel® PH-101) was donated by the FMC Corp. (Newark, DE, USA). Imperial® 500 USP was donated by Luzenac America (Englewood, CO).

5.2.2 Methods

5.2.2.1 Preparation of Core Pellets

Anhydrous theophylline (25%), lactose monohydrate (45%) and microcrystalline cellulose (25%) were passed through a 30-mesh sieve and then mixed 5 minutes. A 12.5% w/v aqueous solution of polyvinylpyrrolidone (equivalent to 5% in the final formulation) was used as a binder in the wet-massing process. The wet mass was extruded using an LCI Benchtop Granulator (Tokyo, JP) at a rotation blade speed of 50 rpm. The extrudates were spheronized at 1000 rpm for 2 minutes using a Caleva Model 120 Spheronizer (Dorset, UK). The pellets were sieved after drying for 24 hours at 40°C and the 16-20 mesh fraction was used for the coating trials.

5.2.2.2 Preparation of Coating Dispersions

A quantity of ethylcellulose polymer was dispersed in water via high shear mixing with a POLYTRON® rotor-stator (Brinkmann Instruments, Westbury, NY, USA), added

to the Eudragit® NE 30 D dispersion, and agitated with a magnetic stir bar for a period of 1 hour. A quantity of Imperial® 500 talc equal to 50% of the dry polymer weight was then dispersed in a separate volume of water via high shear mixing with a POLYTRON®, added to the polymeric blend, and the resulting dispersion was allowed to mix for a further 10 minutes prior to application. The final dispersion had a total solids content of 15%. The composition of the coating formulations is presented in Table 5.1.

5.2.2.3 Coating of Theophylline Cores

A 250-g batch of theophylline pellets was placed in a Strea-1 fluidized-bed coater (Aeromatic-Fielder, Bubendorf, SW). The cores were preheated for 10 minutes at 30°C before coating dispersion was applied. The dispersion was sprayed onto the pellets with a Watson-Marlow 520s peristaltic pump through a 1.2 mm nozzle with an atomizing air pressure of 25 psi. The inlet temperature was 29-30°C and the outlet temperature was 25-27°C. To avoid pellet agglomeration, the dispersion was applied at a rate of 1 g/min until a theoretical weight gain of 2.5% had been reached and the rate was then increased to 3 g/min. The polymeric dispersion was stirred continuously throughout the coating process to prevent the sedimentation of dispersed solids. After coating, the pellets were dusted with 1.25 g of Imperial® 500 talc (0.5% based on the uncoated cores) and placed in a 60°C oven for 18 hours.

5.2.2.4 Stability Testing and In Vitro Drug Release

After curing at 60°C for 18 hours, the coated pellets were placed in aluminum induction-sealed high density polyethylene (HDPE) containers with a 1.0 g MINIPAX molecular sieve (Impak Corporation, Los Angeles, CA) inside the container and stored at 25°C/60% RH or 40°C/75% RH for a period of up to 3 months. Dissolution testing was performed according to the United States Pharmacopoeia (USP) 29 Apparatus II (Vankel

VK 7000, Cary, NC, USA) over a 18-hour period in 900 ml of pH 7.4 (50 mM) phosphate buffer. The paddle speed was 50 rpm and the temperature of the media was maintained at 37±0.2°C.

Dissolution testing was performed in triplicate with 150 mg of coated pellets (containing 30 ± 3 mg theophylline) added to each dissolution vessel. A volume of 5 ml was removed by a Vankel 8000 Autosampler (Cary, NC, USA) after 1, 2, 4, 6, 8, 10, 12, 16, and 18 hours. Infinity samples were obtained by mixing with a high-shear homogenizer (POLYTRON®, Brinkmann Instruments, Westbury, NY, USA) for 1.5 minutes.

The theophylline content of each sample was analyzed using ultraviolet (UV) spectroscopy. A volume of 150 µL was taken from each sample and placed in a corresponding well of a Falcon 96-well UV transparent plate (VWR International, West Chester, PA, USA). An equal volume of pH 7.4 dissolution media was added to each well to ensure that the concentrations were within the analytical range of the instrument. The tray was then loaded into a μQuant 96-Well Plate Reader (Bio-Tek Instruments, Inc., Winooski, VT, USA) and analyzed for theophylline at a wavelength of 273 nm. The amount of theophylline released was calculated by taking the analyte concentration, comparing this to the concentration of the infinity time point, and multiplying by 100 to obtain a percentage of theophylline released at each time point.

5.2.2.5 Free Film Preparation

Eudragit® NE 30 D films were formulated using a 1:1 weight of the polymer dispersion and water (75 g dispersion, 75 g water) to achieve a total solids content of 15%. For films containing Ethocel® 7 FP, the cellulosic polymer was added at a ratio that is half the dry polymer weight of Eudragit® NE 30 D and a volume of water was added to adjust the overall concentration of solids in the dispersion to 15% so that the resulting

films were composed of the same amount of Eudragit® NE 30 D polymer (e.g., to spray 15 g of Eudragit® NE 30 D polymer, 150 g of dispersion was delivered). The Ethocel® 7 FP was dispersed in the water using a POLYTRON® for a period of 1 minute. The dispersion was then added to the Eudragit® NE 30 D and allowed to stir for 1 hour prior to spraying.

The dispersions were applied to a cylinder covered with Bytac® PTFE film rotating at 50 rpm via a Watson-Marlow 520s pump, marprene tubing, and a two fluid spray nozzle (Mini Hi-Coater, Vector Corporation, Marion, IA, USA). The atomizing air pressure was set at 0.3 kg/m^2 and the pump rate was 0.6 rpm (~1 g/min). The spray apparatus provided an oscillatory motion over a 15 cm linear path at 28 rpm. The distance from the nozzle to the rotating cylinder was 12 cm. The temperature was controlled using two infrared heat lamps and set such that the surface of the film remained at a temperature of 25-30°C as measured by an infrared thermometer. An amount of 100 g of the coating dispersion was used to create each Eudragit® NE 30 D film, while 150 g of the coating dispersion was used to create each Eudragit® NE 30 D/Ethocel® 7 FP film. After the spraying process was complete, the films were cured at a temperature of 60°C for a period of 18 hours. The films were then removed from the oven and cut into geometries for either water vapor permeability trials (circular) or physical-mechanical testing trials (rectangular). These films were then placed in desiccators and stored at 25°C or 40°C for stability studies. The films were removed from the stability chambers and allowed to equilibrate at 25°C/50% RH for a period of 72 hours prior to testing.

5.2.2.6 Physico-Mechanical Testing

Stress-strain experiments with the sprayed films were performed using an Instron Model 4201 with a 1000 N load cell. Prior to testing, films were cut into 70 mm x 10

mm strips (n=10). The thickness was measured using a Mitutoyo Model ID-C1012EBS digital micrometer (Mitutoyo Corp., JP) and the average of five different measurements along the length of the film was determined. Stress-strain measurements were conducted on the cut films in accordance with ASTM guideline D 882-02 [17] using a gap distance of 50 mm, load range of 1N and crosshead speed of 25 mm/min. The maximum tensile strength, percent elongation, and modulus of the films were calculated using Bluehill v.2.5 software (Instron, Norwood, MA).

5.2.2.7 Water Vapor Permeability Testing

The water vapor permeability of the sprayed films was determined according to guidelines set forth in ASTM E 96/E 96 - 05 using the desiccant method [18]. The thickness of each film was determined using a Mitutoyo Model ID-C1012EBS digital micrometer by measuring four points along the circumference and one point at the center of a circular sample of film and averaging the values. The film sample was secured to the open mouth of an aluminum permeability cup (4 cm inner diameter and 3 cm depth) containing 20 g of Drierite® desiccant. The permeability cups (n=3) were accurately weighed, placed in a humidity chamber at 23°C/80% RH, and periodically reweighed over 96 hours to determine the weight gain. The water vapor transmission rate (WVT) and permeability (P) were calculated using the following equations [18]:

$$WVT = (G/t)/A \qquad \text{(Eq. 5.1)}$$

$$P = \frac{WVT}{S} \times (R_1 - R_2) \times d \qquad \text{(Eq. 5.2)}$$

where G is the weight change, t is the time during which G occurred, A is the test area (cup mouth area), S is the saturation vapor pressure at test temperature, R_1 and R_2 are

the relative humidity in the test chamber and inside the cup (0% RH for the desiccant method), respectively, and *d* is the thickness of the film.

5.2.2.7 Particle Sizing of Ethylcellulose Powders

The particle size of Ethocel® powders used in the coating formulations were determined using a Malvern Mastersizer® 2000 (Malvern Instruments, Ltd., Worcestershire, UK) with water as the dispersing medium. A nominal amount of ethylcellulose powder was dispersed in deionized water by shaking in a scintillation vial. The dispersion was then added to the apparatus, with recirculation and sonication, until a percent obscurance of between 15% and 30% was acquired. The particle size was reported as the D(v, 0.5).

5.2.2.8 Determination of Thermal Properties

The thermal properties of sprayed films were determined using modulated differential scanning calorimetry (MDSC) via a DSC 2920 (TA Instruments, New Castle, DE, USA). Film samples of 5-10 mg were weighed into aluminum pans and then sealed. The samples were analyzed over a range of -20-180°C with a nitrogen flow rate of 40 ml/min, a heating rate of 12°C/min, and a modulation rate of 0.5°C with a period of 40 seconds. The glass transition temperature (Tg) was determined as the midpoint of the transition using Modulated DSC Analysis V 1.1A software.

5.2.2.9 Scanning Electron Microscopy

To investigate the effect of dissolution media on the surface morphology of the dosage forms, pellets coated with either Eudragit® NE 30 D or a 2:1 ratio of Eudragit® NE 30 D:Ethocel® 7 FP were placed in 900 ml of pH 7.4 (50 mM phosphate) buffered solution and agitated via USP Apparatus II with a paddle rotation speed of 50 rpm and temperature held constant at 37.2°C. After 3 hours, the pellets were separated from the

media with a 100 μm screen and washed with deionized water. The pellets were then placed in a chamber containing desiccant (calcium sulfate) under vacuum for a period of 48 hours. To examine pellets that had not undergone dissolution, the pellets were placed on a 100 μm screen and washed briefly with deionized water to remove any talc that may have adhered to the surface. These pellets were also placed in the desiccated chamber under vacuum for a period of 48 hours. The pellets were secured to an aluminum stage with the use of adhesive carbon tape and coated with gold for 45 seconds in an argon atmosphere. Observation of the surface morphology of the pellets was carried out with the use of Hitachi S-4500 field emission scanning electron microscope.

5.2.2.10 Statistical Analysis

Statistical analysis of *in vitro* dissolution data was measured using the f_2 similarity factor treatment described by Shah, et al. [19]. To ensure that a bias in the f_2 similarity factor was not increased, only one time point above 85% dissolution was utilized, when applicable.

Statistical evaluation of the physico-mechanical properties and water vapor permeability of sprayed films was conducted with Minitab Release 14 software using both the Kruskal-Wallis test (non-parametric, α=0.05) and the one-way analysis of variance (ANOVA) with α=0.05 for a 95% confidence level and Tukey's HSD post hoc test was used to compare the means of each population.

5.3 RESULTS AND DISCUSSION

The effect of particle size of Ethocel® S4 on the release rate of theophylline from pellets coated with a 1:1 aqueous dispersion of Eudragit® NE 30 D:Ethocel® S4 blend (Formulations B and C) is shown in Figure 5.1. It can be seen that as the particle size of Ethocel® S4 decreases from 91 μm to 39 μm, the rate at which theophylline was released from the coated pellets increased. Similar increases in film permeability were also reported by Parker [20] and co-workers when investigating the effect of talc particle size on the water vapor permeability of free films. The researchers found that as the particle size of talc decreased, there was an increase in the permeability of films to moisture. Maul and Schmidt [21] also showed that particle size and morphology of pigments influenced the dissolution rate of bisacodyl from pellets coated with Eudragit® L 30 D. It was found that large, platelet-like additives functioned to decrease the drug release rate when compared to smaller, spherical-shaped particles. Since the size fractions of Ethocel® S4 were 91 μm and 39 μm, it was deemed impractical to continue coating studies with this excipient, as the large particle size of this grade of Ethocel® could interrupt the interfacial bonding between the polymer and the surface of the coated pellet [22]. Subsequent studies utilized Ethocel® 7 FP, which had a particle size range of 5-15 μm, with a mean particle size of 9 μm. It was expected that the small particle size of the Ethocel® 7 FP would further increase the drug release rate if pellets were coated with a formulation of 1:1 Eudragit® NE 30 D:Ethocel® 7 FP; thus, the remaining coating trials were carried out with a formulation of 2:1 Eudragit® NE 30 D:Ethocel® 7 FP.

The effect of Ethocel® 7 FP on the thermal properties of Eudragit® NE 30 D sprayed films was investigated using modulated differential scanning calorimetry (MDSC), and the results are shown in Figure 5.2. The glass transition temperature of

Eudragit® NE 30 D free films alone (curve a) was found to be 12.9°C, which was in close agreement with the glass transition temperature of 11°C reported by the manufacturer [23]. The glass transition temperature of Ethocel® 7 FP powder (curve c) was determined to be 127.8°C, which was in close agreement with previously reported values of 129-133°C [24]. When the thermal properties of 2:1 Eudragit® NE 30 D:Ethocel® 7 FP free films (curve b) were examined, the glass transition temperatures of both the acrylic and cellulosic polymers were prominent and relatively unchanged, as was the melting point endotherm of nonoxynol 100 at 47.12°C; however, a third thermal event was also observed at 103.12°C. Previously published Hansen solubility parameters for Eudragit® NE 30 D and ethylcellulose have demonstrated values of 17.1 $MPa^{1/2}$ [23] and 20-21 $MPa^{1/2}$ [25, 26], respectively. Solubility parameters have previously been used to characterize component miscibility, and differences less than 7.0 $MPa^{1/2}$ were shown to indicate miscibility of components [27]. This suggested that the third thermal event in the MDSC thermogram was a phase consisting of the acrylic and cellulosic polymer.

The Gordon-Taylor equation (equation 5.3) [28] has been used in previous studies to determine the glass transition temperature of miscible polymer blends [29], and was applied here to calculate the composition of the third phase in the film with T_{g12} defined as the glass transition of the thermal event, w_1 and T_{g1} being the weight fraction and glass transition temperature of the material with the lower glass transition temperature, w_2 and T_{g2} being the weight fraction and glass transition temperature of the material with the higher glass transition temperature, and K being the ratio of T_{g12}'s components, $K = T_{g1}/T_{g2}$.

$$T_{g12} = \frac{[w_1 T_{g1} + K w_2 T_{g2}]}{[w_1 + K w_2]} \qquad \text{(Eq. 5.3)}$$

Assuming that the fraction of nonoxynol 100 in the film is negligible, the third phase is composed of only ethylcellulose and the acrylic polymer such that:

$$1 = w_2 + w_1 \qquad \text{(Eq. 5.4)}$$

upon rearrangement,

$$w_2 = \frac{-1(T_{g12} - T_{g1})}{(-T_{g12} + KT_{g12} + T_{g1} - KT_{g2})} \qquad \text{(Eq. 5.5)}$$

and

$$w_1 = 1 - w_2 \qquad \text{(Eq. 5.6)}$$

When the data from thermal analysis were applied to this equation, it was found that this third phase was composed of 85% ethylcellulose and 15% acrylic polymer; however, this third phase was determined to be a small fraction of the overall composition by evaluation of the specific heat profile, suggesting that the two polymers were substantially immiscible.

Physico-mechanical properties have been reported in the literature to investigate the aging phenomena of polymeric films [30-33]. Further coalescence and inter-diffusion of the polymer chains during storage results in decreased elongation and increased modulus of the films [33]. When investigating the physico-mechanical properties of sprayed films containing a 2:1 blend of Eudragit® NE 30 D:Ethocel® 7 FP, there was no statistically significant change in either elongation (Figure 5.3(a)) or modulus (Figure 5.3(b)), indicating that further coalescence of the acrylic polymer was hindered by the presence of the fine particle ethylcellulose. Analysis of moduli by ANOVA gave p-values of 0.234 and 0.328 for films stored at 25°C and 40°C, respectively; while analysis

of moduli via non-parametric methods (Kruskal-Wallis) gave p-values of 0.089 and 0.098 for films stored at 25°C and 40°C, respectively.

Physical aging of polymers can also produce changes in the permeability of free films [32, 33]. Decreases in this parameter are due to changes in both porosity and tortuosity of the polymer, indicating densification of the film. The data presented in Figure 5.4 show that films composed of Eudragit® NE 30 D:Ethocel® 7 FP (2:1) exhibited a higher permeability than films of Eudragit® NE 30 D alone at the initial time point, indicating that the films containing ethylcellulose were more permeable. The films containing the blend of Eudragit® NE 30 D and Ethocel® 7 FP, when stored at 25°C for a period of up to 1 month, showed no statistical change in permeability from the initial values ($p = 0.089$ for ANOVA, $p=0.108$ for Kruskal-Wallis) and indicated that the films were stable. The decrease in permeability seen in films of the same composition stored at 40°C was statistically significant ($p=0.002$ for ANOVA, $p=0.024$ for Kruskal-Wallis); however, the magnitude of change was very small when compared to those films consisting of only Eudragit® NE 30 D which had been stored at 40°C. Thus, it was expected that any variations observed in the dissolution rate of theophylline pellets coated with a blend of the acrylic and cellulosic polymer stored at these conditions would be minimal.

The application of a 7.5% weight gain of Eudragit® NE 30 D (Formulation A) to the theophylline pellets resulted in less than 20% drug dissolution in pH 7.4 (50 mM phosphate) buffer during 18 hours of dissolution. The addition of 50% Ethocel® 7 FP (based on the dry polymer weight of the acrylic) (Formulation D) significantly increased the drug dissolution rate so that approximately 60% theophylline was released at the 18 hour time point (Figure 5.5) and resulted in a zero-order drug release profile. Both formulations have the same amount of Eudragit® NE 30 D applied to the dosage forms,

with those containing Eudragit® NE 30 D having a 7.5 % total polymer weight gain and those containing Ethocel® having a total polymer weight gain (the sum of the acrylic and cellulosic polymers) of 15%. This increase in drug dissolution rate was due to the formation of channels in the films of coated dosage forms as seen in Figure 5.6. The scanning electron micrographs in Figure 5.6(a) and Figure 5.6(c) show the surface morphology of film-coated theophylline pellets before dissolution testing. Both pellets exhibit smooth surfaces prior to testing; the plate-like particles on the surface were identified as talc, which was added to prevent the sticking of the pellets during coating. There was a noticeable change between the two formulations following dissolution. The pellets coated with only Eudragit® NE 30 D (Figure 5.6(d)) continued to exhibit a smooth surface, while those coated with a formulation containing Ethocel® 7 FP (Figure 5.6(b)) showed the formation of pores and channels, which served to increase the dissolution of theophylline from the drug containing core. The increase in drug release rate corresponded well with the enhanced permeability of sprayed films noted from the water vapor permeability studies.

The stability (with respect to drug release rate) of coated pellets was determined by placing the dosage forms in aluminum induction sealed HDPE containers with desiccant at storage conditions of both 25°C/60% RH (Figure 5.7) and 40°C/75% RH (Figure 5.8). When the pellets were stored at the lower temperature, the theophylline release rate was stable over the course of 3 months, with an f_2 similarity factor of 85. Likewise, when stored at 40°C/75% RH the drug release rate was also stable, with an f_2 similarity factor of 81. The water vapor permeability studies of sprayed films showed a small decrease in the permeability for Eudragit® NE 30 D: Ethocel® 7 FP films stored at 40°C; however, as expected, a decrease in drug release rate was not observed in the film-coated dosage forms.

5.4 CONCLUSIONS

The rate of drug release was found to be influenced by the particle size of EC used in the coating formulations, with the smaller particle size creating more permeable films and a faster drug release rate. The investigation of thermal data indicated a minimal amount of miscibility between the two polymers, with this miscible phase occupying only a small part of the overall composite. Scanning electron microscopy confirmed the presence of pores and channels in the film during dissolution which allowed drug molecules to easily diffuse through the coating. Stabilization of the drug release rate from the coated dosage forms was attributed to constant water vapor permeability values and maintenance of the physico-mechanical properties of sprayed films. The results from this study suggest that the addition of fine particle ethylcellulose prevents the densification and further coalescence of the acrylic polymer at conditions where were significantly above the glass transition temperature.

5.5 REFERENCES

1. Amighi, K. and A.J. Moës. Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit® RS 30 D film-coated sustained-release theophylline pellets. European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42** (1): p. 29-35.

2. Amighi, K. and A.J. Moës. Influence of curing conditions on the drug release rate from Eudragit® NE 30 D film coated sustained-release theophylline pellets. S.T.P. Pharma Sci, 1997. **7** (2): p. 141-147.

3. Wesseling, M. and R. Bodmeier. Influence of Plasticization Time, Curing Conditions, Storage Time, and Core Properties on the Drug Release from Aquacoat-Coated Pellets. Pharm. Dev. Tech., 2001. **6** (3): p. 325-331.

4. Arno, E.A., P. Anand, K. Bhaskar, S. Ramachandran, M. Saravanan, and R. Vinod. Eudragit® NE 30 D Based Metformin/Gliclazide Extended Release Tablets: Formulation, Characterisation, and *in Vitro* Release Studies. Chem Pharm Bull, 2002. **50** p. 1495-1498.

5. Pozharitskaya, O. and V. Vainshtein. Controlled release of pentoxifylline from polymeric matrices. Pharmaceutical Chemistry Journal, 1998. **32** (8): p. 440-442.

6. Ojoe, E., E.M. Miyauchi, T.C. Viviani, and V.O. Consiglieri. Formulation and in vitro evaluation of theophylline-Eudragit® sustained-release tablets. Rev. Bras. Cienc. Farm., 2005. **41** p. 377-384.

7. Radtke, G., K. Knop, and B.C. Lippold. Manufacture of Slow-Release Matrix Granules by Wet Granulation with an Aqueous Dispersion of Quaternary Poly(meth)acrylates in the Fluidized Bed. Drug Development and Industrial Pharmacy, 2002. **28** (10): p. 1295-1302.

8. Krajacic, A. and I.G. Tucker. Matrix formation in sustained release tablets: possible mechanism of dose dumping. International Journal of Pharmaceutics, 2003. **251** (1-2): p. 67-78.

9. Khamanga, S.M. and R.B. Walker. Evaluation of Rate of Swelling and Erosion of Verapamil (VRP) Sustained-Release Matrix Tablets. Drug Development and Industrial Pharmacy, 2006. **32** (10): p. 1139-1148.

10. Hu, L.-D., Y. Liu, X. Tang, and Q. Zhang. Preparation and in vitro/in vivo evaluation of sustained-release metformin hydrochloride pellets. European Journal of Pharmaceutics and Biopharmaceutics, 2006. **64** (2): p. 185-192.

11. Bajdik, J., K. Pintye-Hodi, O. Planinsek, Z. Tuske, L. Tasic, G. Regdon, S. Srcic, and I. Eros. Surface Treatment of Indomethacin Agglomerates with Eudragit®. Drug Development and Industrial Pharmacy, 2004. **30** (4): p. 381-388.

12. Watano, S., K. Ando, K. Miyanami, Y. Ii, and S. Sasatani. Preparation of core particles for aqueous film coating using agitation fluidized bed. Chem Pharm Bull (Tokyo), 1997. **45** (12): p. 2039-42.

13. Lin, A.Y., N.A. Muhammad, D. Pope, and L.L. Augsburger. A Study on the Effects of Curing and Storage Conditions on Controlled Release Diphenhydramine HCl Pellets Coated with Eudragit® NE 30 D. Pharm. Dev. Tech., 2003. **8** (3): p. 277-287.

14. Zheng, W. and J.W. McGinity. Influence of Eudragit® NE 30 D Blended with Eudragit® L 30 D-55 on the Release of Phenylpropanolamine Hydrochloride from Coated Pellets. Drug Development and Industrial Pharmacy, 2003. **29** (3): p. 357-366.

15. Lin, A.Y. and L.L. Augsburger. Study of Crystallization of Endogenous Surfactant in Eudragit® NE 30 D-Free Films and Its Influence on Drug-Release Properties of Controlled-Release Diphenhydramine HCl Pellets Coated with Eudragit NE 30 D. AAPS PharmSci., 2001. **3** (2):

16. Bajdik, J., K. Pintye-Hodi, G.J. Regdon, P. Fazekas, P. Szabo-Revesz, and I. Eros. The effect of storage on the behaviour of Eudragit® NE free film. Journal of Thermal Analysis and Calorimetry, 2003. **73** (2): p. 607-613.

17. ASTM. ASTM D 882-02 : Standard Test Method for Tensile Properties of Thin Plastic Sheeting. American Society for Testing Materials, 2002

18. ASTM. ASTM E 96/E 96 M-05: Standard Test Methods for Water Vapor Transmission of Materials. American Society for Testing Materials, 2005

19. Shah, V.P., Y. Tsong, P. Sathe, and J.-P. Liu. *In Vitro* Dissolution Profile Comparison - Statistics and Analysis of the Similariry Factor, f_2. Pharmaceutical Research, 1998. **15** (6): p. 889-896.

20. Parker, J.W., G.E. Peck, and G.S. Banker. Effects of solids-loading on moisture permeability coefficients of free films. J Pharm Sci, 1974. **63** (1): p. 119-25.

21. Maul, K.A. and P.C. Schmidt. Influence of different-shaped pigments on bisacodyl release from Eudragit L 30 D. International Journal of Pharmaceutics, 1995. **118** (1): p. 103-112.

22. Felton, L.A. and J.W. McGinity. Influence of pigment concentration and particle size on adhesion of an acrylic resin copolymer to tablet compacts. Drug Development and Industrial Pharmacy, 1999. **25** (5): p. 597-604.

23. Degussa. Innovative formulations from melt extrusions. Degussa GmbH Pharma Polymers, Darmstadt, Germany, 2007

24. Dow. Ethocel®: Ethylcellulose polymers technical handbook. Dow Cellulosics, Midland, MI, USA, 2005

25. Vesey, C.F., T. Farrell, and A.R. Rajabi-Siahboomi. - Evaluation of plasticizers for Surelease®, an aqueous ethylcellulose dispersion for modified release film-coating. - The 32nd Annual Meeting and Exposition of the Controlled Release Society, Miami Beach, FL, 18 June/22 June 2005.

26. Chan, A., K. Coppens, M. Hall, V. He, P. Jog, P. Larsen, B. Koblinksi, M. Read, D. Rothe, S. Somasi, and U. Shrestha. - Solubility parameters as a tool to predict API morphology in hot melt extruded (HME) formulations containing ethycellulose, hypromellose, and polyethylene oxide. - 2006 American Association of Pharmaceutical Scientists Annual Meeting and Exposition, San Antonio, TX, 29 October/ 2 November 2006.

27. Forster, A., J. Hempenstall, I. Tucker, and T. Rades. Selection of excipients for melt extrusion with two poorly water-soluble drugs by solubility parameter calculation and thermal analysis. International Journal of Pharmaceutics, 2001. **226** (1-2): p. 147-161.

28. Gordon, M. and J.S. Taylor. Ideal copolymers and the second-order transitions of synthetic rubbers. I. Noncrystalline copolymers. Journal of Applied Chemistry, 1952. **2** p. 493-500.

29. Schneider, H. The Meaning of the Glass Temperature of Random Copolymers and Miscible Polymer Blends. Journal of Thermal Analysis and Calorimetry, 1999. **56** (3): p. 983-989.

30. Guo, J.-H., R.E. Robertson, and G.L. Amidon. Influence of Physical Aging on Mechanical Properties of Polymer Free Films: The Prediction of Long-Term Aging Effects on the Water Permeability and Dissolution Rate of Polymer Film-Coated Tablets. Pharmaceutical Research, 1991. **8** (12): p. 1500-1504.

31. Gutierrez-Rocca, J.C. and J.W. McGinity. Influence of Physical Aging on the Physical-Mechanical Properties of Acrylic Resin Films Cast from Aqueous Dispersions and Organic Solutions. Drug Dev. Ind. Pharm., 1993. **19** (3): p. 315-332.

32. Kucera, S.A., N.H. Shah, A.W. Malick, M.A. Infeld, and J.W. McGinity. The Use of Proteins to Minimize the Physical Aging of Eudragit® Sustained Release Films. Drug Development and Industrial Pharmacy, 2007. **33** (7): p. 717-726.

33. Zheng, W., D. Sauer, and J.W. McGinity. Influence of hydroxyethylcellulose on the drug release properties of theophylline pellets coated with Eudragit® RS 30 D. European Journal of Pharmaceutics and Biopharmaceutics, 2005. **59** (1): p. 147-154.

5.6 TABLES

Formulation	A	B	C	D
Eudragit® NE 30 D	68.75	68.75	68.75	68.75
Ethocel® S4	0	20.63	20.63	0
Ethocel® S7 FP	0	0	0	10.31
Imperial® 500	10.31	20.63	20.63	15.47
Water	127.19	302.5	302.5	214.84
Total	206.25	412.51	412.51	309.37

Table 5.1 Composition of polymeric dispersions used in coating experiments (all diluted with water to 15% solids and adjusted for a 10% overage).

5.7 FIGURES

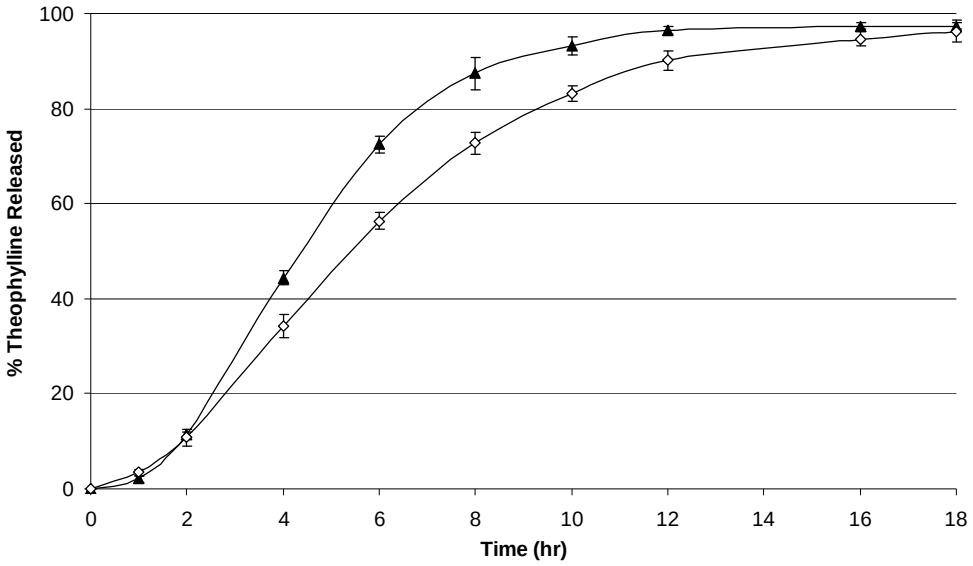


Figure 5.1 The influence of Ethocel® S4 particle size (▲ - 39 µm, ◇ - 91 µm) on the release of theophylline from pellets coated with a 15% weight gain of Eudragit® NE 30 D:Ethocel® S4 (1:1) and 50% Imperial® 500 talc (USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, *n*=3)

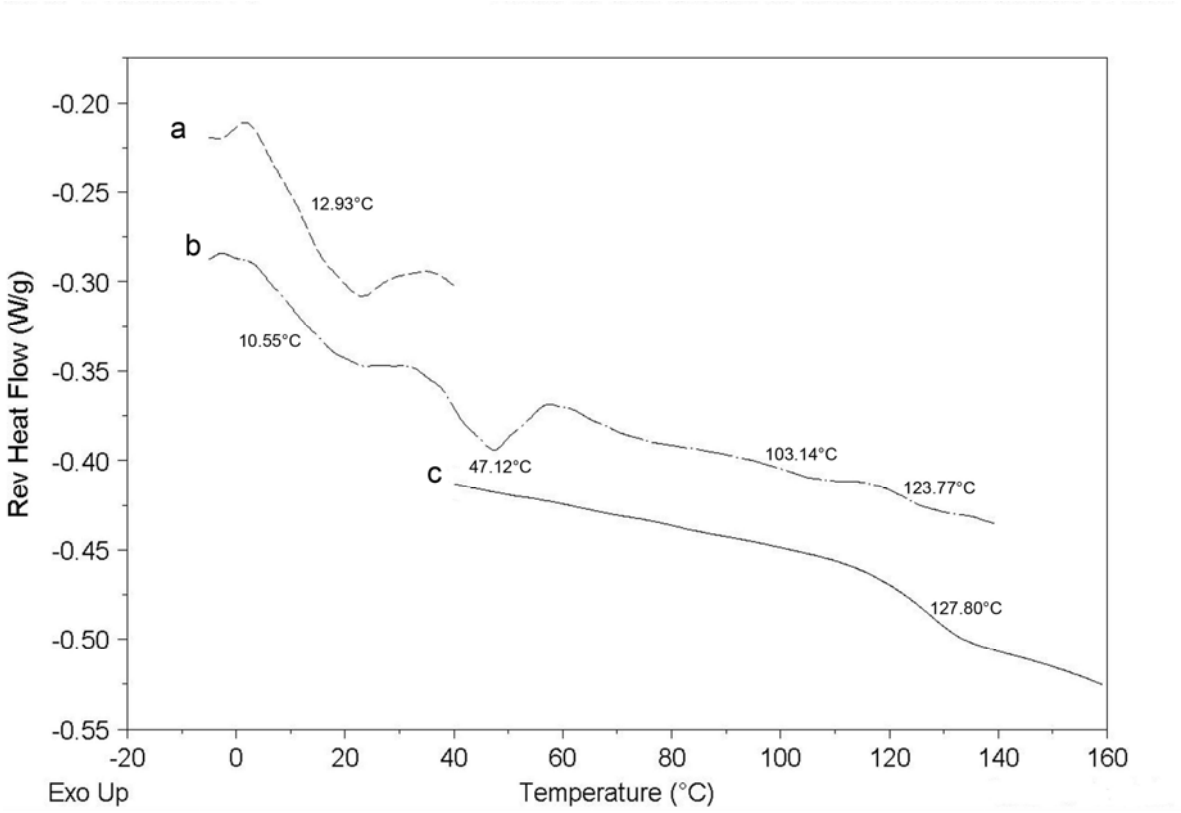
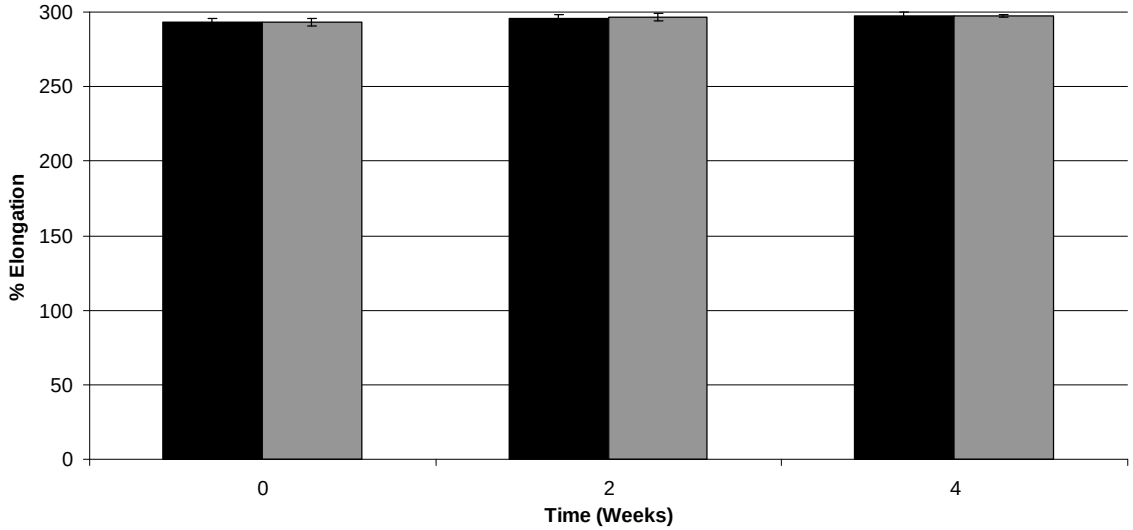


Figure 5.2 Modulated differential scanning calorimetry (MDSC) thermograms of (a.) Eudragit® NE 30 D; (b.) Eudragit® NE 30 D:Ethocel® 7 FP (2:1); (c.) Ethocel® 7 FP.

(a.)



(b.)

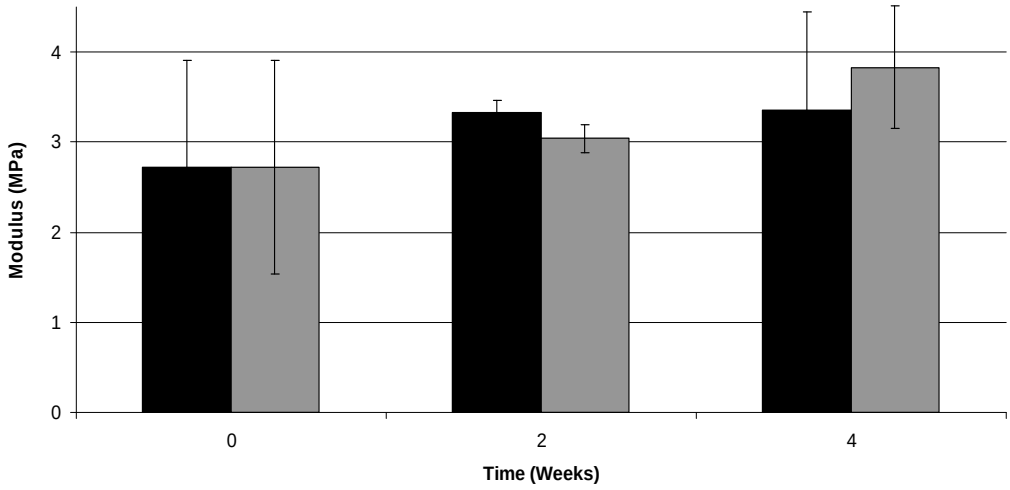


Figure 5.3 The influence of time and temperature on the physico-mechanical properties of sprayed films containing Eudragit® NE 30 D:Ethocel® 7 FP (2:1), (a.) % Elongation; (b.) Modulus. (■, 25°C, ■, 40°C)

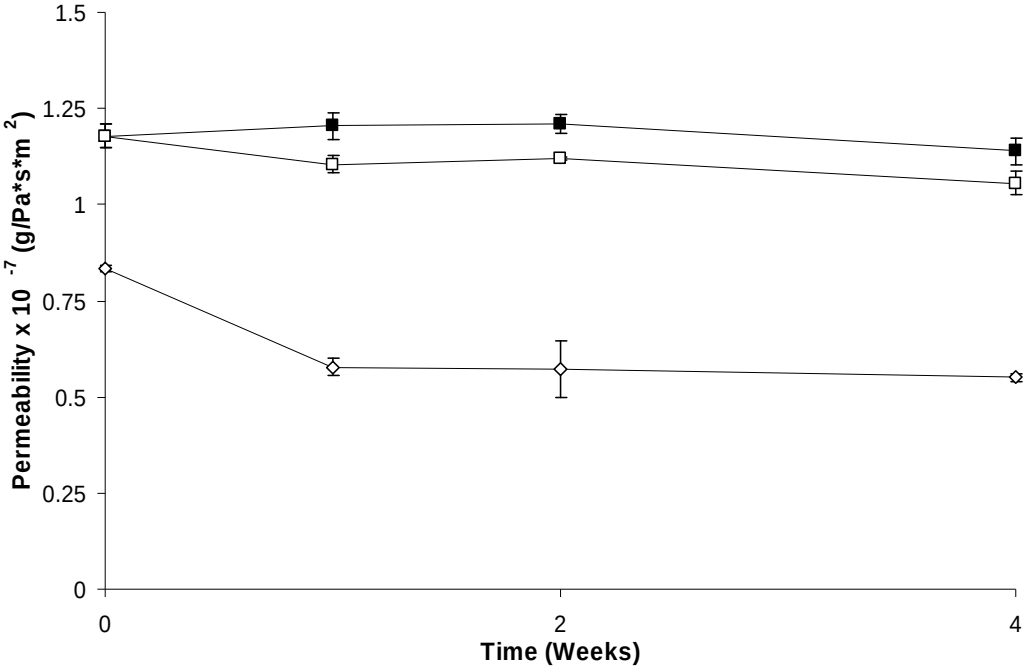


Figure 5.4 The effect of temperature and time on the water vapor permeability of sprayed films containing Eudragit® NE 30 D:Ethocel® 7 FP (2:1) (■, 25°C, □, 40°C) or Eudragit® NE 30 D only (◇, 40°C) (tested at 25°C/80% RH, *n*=3).

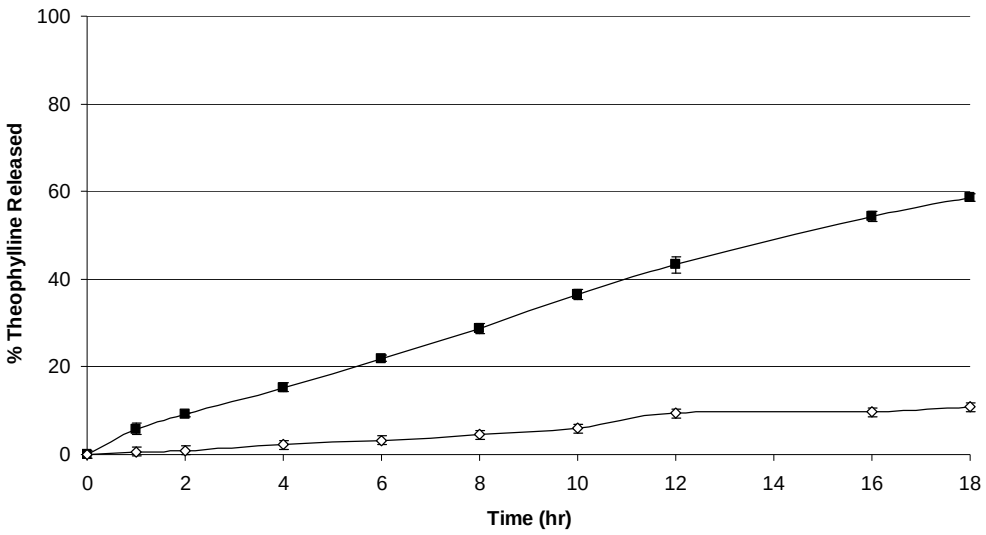


Figure 5.5 The influence of Ethocel® 7 FP addition on the release of theophylline from coated pellets (■ - Eudragit® NE 30 D:Ethocel 7 FP (2:1), 50% Imperial® 500 talc, 15% W.G.; ◇ - Eudragit® NE 30 D, 50% Imperial® 500 talc, 7.5% W.G.) (USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, *n*=3).

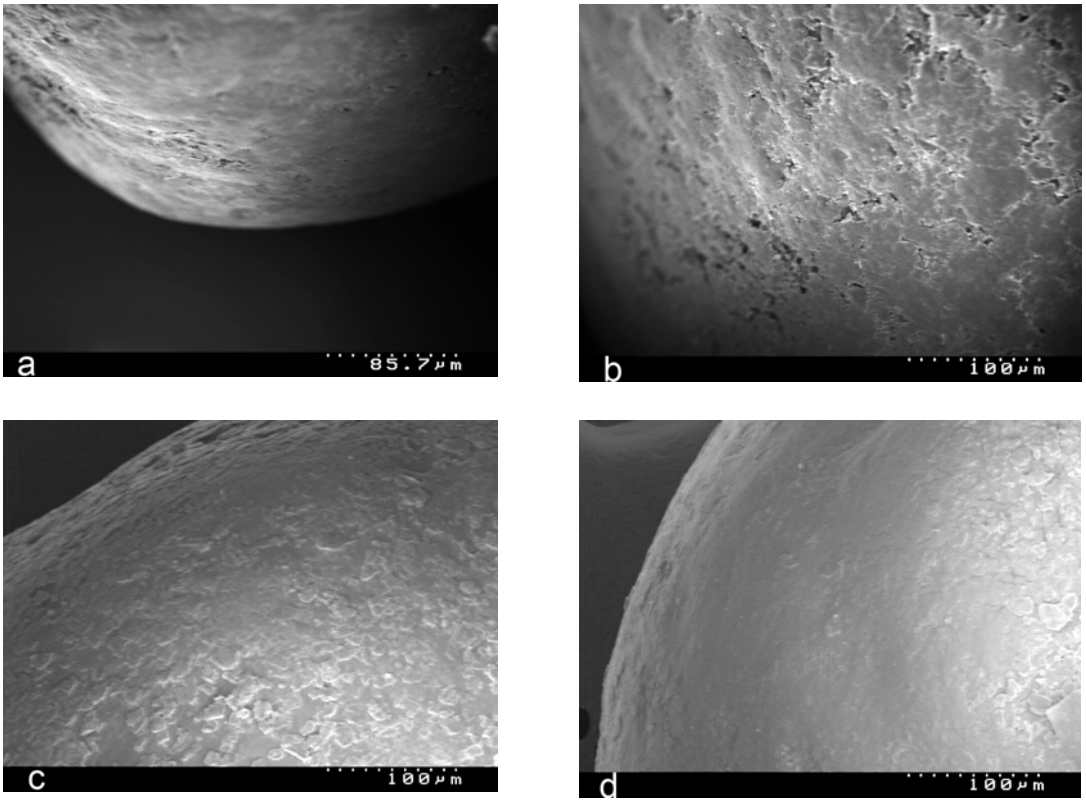


Figure 5.6 Scanning electron micrographs of pellets coated with Eudragit® NE 30 D:Ethocel® 7 FP (2:1): (a.) before dissolution, (b.) after 3 hours dissolution; and pellets coated with Eudragit® NE 30 D: (c.) before dissolution, (d.) after 3 hours dissolution. (USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C).

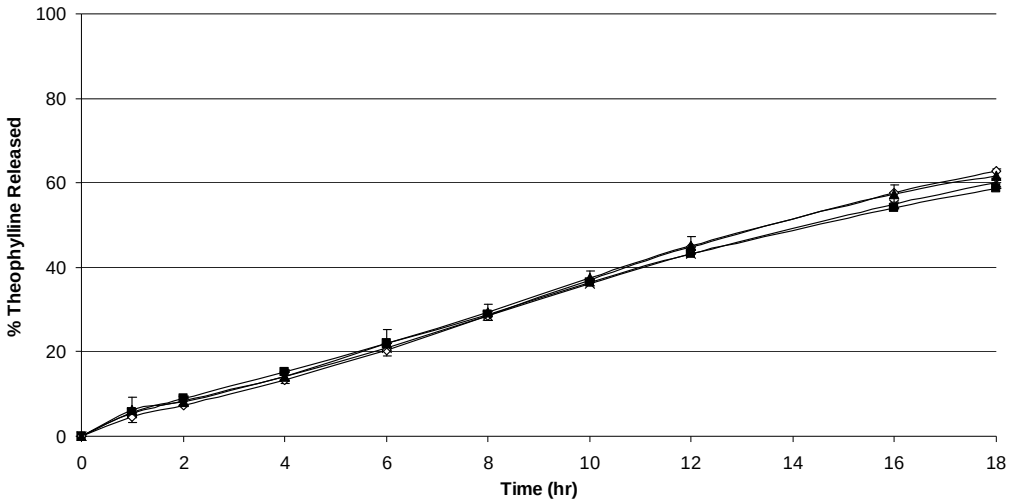


Figure 5.7 The influence of storage time on the release of theophylline (30 mg) from pellets coated with Eudragit® NE 30 D:Ethocel® 7 FP (2:1) and 50% Imperial® 500 talc coated to a 15% weight gain and stored in sealed HDPE containers with desiccant at 25°C/60% RH (■ - initial, ◇ - 2 week, × - 1 month, ▲ – 3 month)(USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, n=3).

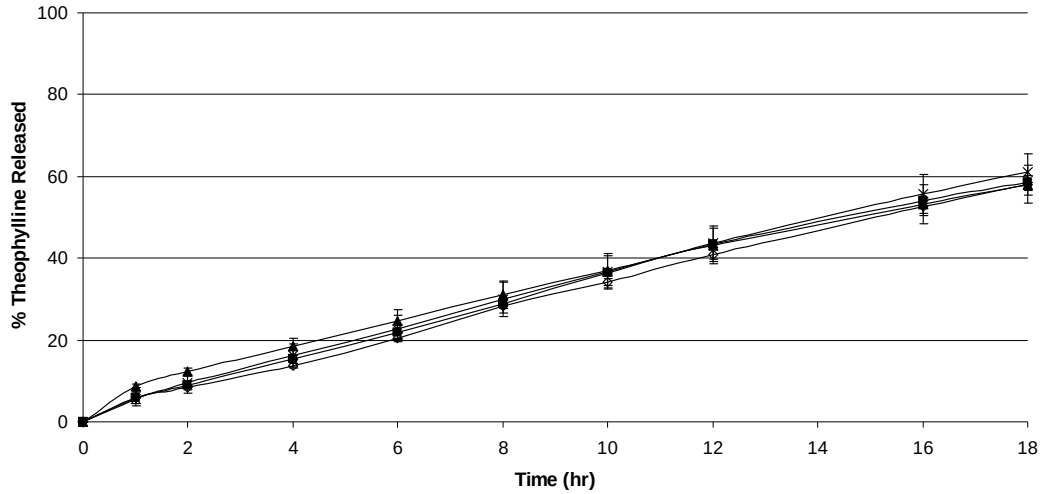


Figure 5.8 The influence of storage time on the release of theophylline (30 mg) from pellets coated with Eudragit® NE 30 D:Ethocel® 7 FP (2:1) and 50% Imperial® 500 talc coated to a 15% weight gain and stored in sealed HDPE containers with desiccant at 40°C/75% RH (■ - initial, ◇ - 1 month, × - 2 month, ▲ – 3 month)(USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, *n*=3).

Chapter 6: Influence of an Acrylic Polymer Blend on the Physical Stability of Film-Coated Theophylline Pellets

Abstract:

The purpose of this study was to investigate the physical stability of a coating system consisting of a blend of two sustained-release acrylic polymers and its influence on the drug release rate of theophylline from coated pellets. Eudragit® RS 30 D was plasticized by the addition of Eudragit® NE 30 D and the predicted glass transition temperature (Tg) of the blend was similar to the experimental values. Sprayed films composed of a blend of Eudragit® NE 30 D:Eudragit® RS 30 D (1:1) showed a water vapor permeability value six times greater than those films containing only Eudragit® NE 30 D due to the presence of quaternary ammonium functional groups that increased the swellability of the polymer blend. The films prepared from the blend exhibited stable permeability values when stored for 1 month at both 25°C and 40°C, while the films which were composed of only Eudragit® NE 30 D showed a statistically significant decrease in this parameter when stored under the same conditions. Eudragit® NE 30 D:Eudragit® RS 30 D (1:1) sprayed films decreased in elongation from 180% to 40% after storage at 40°C for 1 month, while those stored at 25°C showed no change in elongation during the same study. In coated pellets, the addition of Eudragit® RS 30 D to the Eudragit® NE 30 D increased the theophylline release rate and the pellets were stable when stored at 25°C for a period of up to 3 months due to maintenance of the physico-mechanical elongation of the film. Those pellets stored at 40°C exhibited a decrease in drug release rate over time as a result of changes in film physico-mechanical properties which was attributed to further coalescence and densification of the polymer. When storage conditions were above the Tg of the composite, instabilities in both drug release

rate and physical properties were evident. Stabilization in drug release rate from coated pellets could be correlated with the physico-mechanical stability of the film formulation when stored at temperatures below the Tg of the polymer.

6.1 INTRODUCTION

The coating of dosage forms with aqueous latex or pseudolatex dispersions is a common manufacturing process utilized in designing sustained release dosage forms. Both acrylic- and cellulosic-based polymer systems have been used as excipients for modified release coatings in this regard. While the use of these aqueous coating systems is advantageous in some respect, both systems have inherent problems in that films formed by these polymers can undergo an aging process, resulting in physically unstable films as a function of time, temperature, and relative humidity [1-5].

The physical aging of polymeric films is a problem that both polymer scientists and chemical engineers have been aware of for many years. Struik [6] has reported that the driving force for aging in amorphous polymers is the movement towards a thermodynamic equilibrium. As a result of being essentially "locked" in place at temperatures below the glass transition temperature (Tg) of the material, the polymer possesses an enthalpy and free volume that is much greater than at equilibrium. Since the molecular mobility of the polymer is not zero, the free volume of the material will continue to decrease slowly over time until equilibrium is reached. This densification of the polymer results in changes in the diffusivity of the membrane.

Drug release from pellets coated with insoluble polymers follows Fick's First Law of Diffusion, as seen in equation 6.1, where Q is the amount of drug that has diffused through the film as a function of time t, h is the thickness of the film, D is the diffusion coefficient of the API, S is the area available for diffusion, C_1 is the concentration of drug in the dosage form, and C_2 is the concentration of drug in the dissolution medium.

$$Q = \frac{DS(C_1 - C_2)t}{h} \qquad \text{(Eq. 6.1)}$$

The changes in the film's porosity and tortuosity during aging was later related to D by Iyer and associates [7] through equation 6.2, where D_w is the diffusion coefficient of the drug in water and e and τ are the porosity and tortuosity of the film, respectively.

$$D = \frac{D_w(e)}{\tau} \qquad \text{(Eq. 6.2)}$$

Thus during aging, the variation in diffusivity is a direct consequence of diminishing porosity and increasing tortuosity of the polymeric film coating.

Several strategies have been proposed to resolve the problem of physical aging in acrylic polymers that have been employed for the film coating of sustained release dosage forms. These include the addition of high levels of plasticizer [1] or talc [8], the inclusion of immiscible, water soluble non-ionic excipients [5] or proteins [9], and the addition of silicon dioxide to the polymeric coating formulation [10]. Another avenue of research that has been described in previous reports is the blending of high Tg polymers which are miscible with the functional coating. Wu and coworkers [11] found that a blend of Eudragit® RS 30 D and Eudragit® L 100-55 at a 3:1 ratio provided a stable release rate of theophylline from coated pellets when the dosage forms were stored at 40°C. The two materials formed a miscible composite that had a Tg of 44°C and the mechanism of stabilization was due to a decrease in the molecular mobility of polymer chains in the film. In a similar study [12], Zheng and coworkers investigated the influence of Eudragit® L 30 D-55 on the stability of Eudragit® NE 30 D films. They reported that films of a 5:1 blend of Eudragit® NE 30 D:L 30 D-55 equilibrated over a shorter period of time and that the release rate of phenylpropanolamine hydrochloride from pellets coated with the polymeric blend showed improved stability when compared to pellets coated with a formulation containing only Eudragit® NE 30 D.

The objective of the present study was to investigate the effect of blending Eudragit® NE 30 D with Eudragit® RS 30 D on the drug release rate and physical stability of coated theophylline pellets. The thermal properties of the components in the resulting mixture were examined, as were the physico-mechanical parameters (elongation) and water vapor permeability of sprayed films. It was hypothesized that the addition of Eudragit® RS 30 D would stabilize the drug release rate by raising the Tg of Eudragit® NE 30 D to the point that film aging would be impeded without compromising the film formation during processing.

6.2 MATERIALS AND METHODS

6.2.1 Materials

Eudragit® NE 30 D and Eudragit® RS 30 D dispersions were donated by Degussa, Röhm America (Piscataway, NJ, USA). Anhydrous theophylline and lactose monohydrate were both purchased from Spectrum Chemical (Gardena, CA, USA). Polyvinylpyrrolidone (Kollidon® K-30) was donated by the BASF Corp. (Mount Olive, NJ, USA). Microcrystalline cellulose (Avicel® PH-101) was donated by the FMC Corp. (Newark, DE, USA). Imperial® 500 USP was generously donated by Luzenac America (Englewood, CO).

6.2.2 Methods

6.2.2.1 Preparation of Core Pellets

Anhydrous theophylline (25%), lactose monohydrate (45%) and microcrystalline cellulose (25%) were passed through a 30-mesh sieve and then mixed 5 minutes. A 12.5% w/v aqueous solution of polyvinylpyrrolidone (equivalent to 5% in the final formulation) was used as a binder in the wet-massing process. The wet mass was extruded using an LCI Benchtop Granulator (Tokyo, JP) at a rotation blade speed of 50

rpm. The extrudates were spheronized at 1000 rpm for 2 minutes using a Caleva Model 120 Spheronizer (Dorset, UK). The pellets were sieved after drying for 24 hours at 40°C, and the 16-20 mesh fraction was used for the coating trials.

6.2.2.2 Preparation of Coating Dispersions

An equal amount of Eudragit® NE 30 D and Eudragit® RS 30 D dispersions (45.83 g of each) were added to a beaker, placed on a magnetic stir plate, and mixed with slow agitation for a period of one hour. 13.75 g of Imperial® 500 talc (equal to 50% of the dry polymer weight) was added in a separate volume of water (170.0 g) and dispersed via high shear mixing with a POLYTRON®. The talc dispersion was added to the acrylic blend. The resulting dispersion had a total solids content of 15% and was allowed to mix for a further 10 minutes prior to application to the theophylline pellets. The final dispersion had a total solids content of 15%.

Eudragit® NE 30 D coating dispersions were prepared by first adding 68.75 g of the polymeric latex to a beaker. A POLYTRON® high shear mixer was used to disperse 10.31 g of Imperial® 500 talc (equal to 50% of the dry polymer weight) in 127.19 g of water. The talc dispersion was added to the acrylic latex with gentle stirring by a magnetic bar and stir plate and allowed to mix for 10 minutes prior to coating. The final dispersion had a total solids content of 15%.

6.2.2.3 Coating of Theophylline Cores

A 250-g batch of theophylline pellets was placed in a Strea-1 fluidized-bed coater (Aeromatic-Fielder, Bubendorf, SW) and preheated for 10 minutes at 30°C before the coating process. The dispersion was delivered with a Watson-Marlow 520s peristaltic pump through marprene tubing. A 1.2 mm nozzle was used with an atomizing air pressure of 25 psi. The inlet temperature was maintained at 29-30°C and the outlet

temperature was 25-27°C. The dispersion was applied at a rate of 1 g/min, to avoid pellet agglomeration, until a theoretical weight gain of 2.5% had been reached. At this time, the application rate was increased to 3 g/min. To prevent the sedimentation of dispersed solids, the polymeric dispersion was stirred continuously throughout the coating process. After coating, the pellets were dusted with 1.25 g of Imperial® 500 talc (0.5% based on the uncoated cores) and cured in a 60°C oven for 18 hours.

6.2.2.4 Stability Testing and In Vitro Drug Release

After curing, the coated pellets were placed in aluminum induction-sealed high density polyethylene (HDPE) containers with 1.0 g MINIPAX molecular sieve (Impak Corporation, Los Angeles, CA) inside the container and stored at both 25°C/60% RH and 40°C/75% RH for a period of up to 3 months. Dissolution testing was performed according to the United States Pharmacopoeia (USP) 29 Apparatus II (Vankel VK 7000, Cary, NC, USA) over a 18-hour period in 900 ml of pH 7.4 (50 mM) phosphate buffer. The paddle speed was 50 rpm and the temperature of the media was maintained at 37±0.2°C.

Dissolution testing was performed in triplicate with 150 mg of coated pellets (containing 30 ± 3 mg API) added to each dissolution vessel. A volume of 5 ml was removed by a Vankel 8000 Autosampler (Cary, NC, USA) at each sampling time point. Infinity samples were obtained by mixing with a high-shear homogenizer (POLYTRON®, Brinkmann Instruments, Westbury, NY, USA) for 1.5 minutes

The theophylline content of each sample was analyzed using ultraviolet (UV) spectroscopy. A volume of 150 µL was taken from each sample and placed in a corresponding well of a Falcon 96-well UV transparent plate (VWR International, West Chester, PA, USA). An equal volume of pH 7.4 dissolution media was added to each well to ensure that the concentrations were in the linear range of the analytical method.

The tray was then loaded into a μQuant 96-Well Plate Reader (Bio-Tek Instruments, Inc., Winooski, VT, USA) and analyzed for theophylline at a wavelength of 273 nm. The amount of theophylline released was calculated by taking the analyte concentration, comparing this to the concentration of the infinity time point, and multiplying by 100 to obtain a percentage of theophylline released at each time point.

6.2.2.5 Free Film Preparation

Free films were sprayed using a 1:1 ratio of Eudragit® NE 30 D and Eudragit® RS 30 D, which was then diluted with an equal amount of water to achieve a total solids content of 15%. This dispersion was then allowed to mix with gentle agitation via a magnetic stir plate and stir bar for a period of one hour prior to film spraying. For films containing only Eudragit® NE 30 D, the polymer dispersion was diluted with an equal amount of water to achieve a solids content of 15%.

The dispersion was sprayed onto a cylinder covered with Bytac® PTFE film rotating at 50 rpm via a Watson-Marlow 520s pump, marprene tubing, and a two fluid spray nozzle (Mini Hi-Coater, Vector Corporation, Marion, IA, USA). The atomizing air pressure was set at 0.3 kg/m^2 and the pump rate was 0.6 rpm (~1 g/min). The spray apparatus provided an oscillatory motion over a 15 cm linear path at 28 rpm. The distance from the nozzle to the rotating cylinder was 12 cm. The temperature was controlled using two infrared heat lamps. The temperature was set such that the surface of the film was maintained at a temperature of 25-30°C as measured by an infrared thermometer. An amount of 100 g of the coating dispersion was used to create each composite film. After the spraying process was completed, the films were cured at a temperature of 60°C for a period of 18 hours. The films were then removed from the oven and cut into specimens for either water vapor permeability trials (circular) or physical-mechanical testing trials (rectangular). These films were then placed in

desiccators and stored at 25°C or 40°C for stability studies. Prior to investigating the physico-mechanical properties or water vapor permeability, the films were removed from the storage chambers and allowed to equilibrate at 25°C/50% RH for a period of 72 hours.

6.2.2.6 Water Vapor Permeability Testing

The water vapor permeability of the sprayed films was determined according to guidelines set forth in ASTM E 96/E 96 - 05 using the desiccant method [13]. The thickness of each film was determined using a Mitutoyo Model ID-C1012EBS digital micrometer by measuring four points along the circumference and one point at the center of a circular sample of film and averaging the values. The film specimen was secured to the open mouth of an aluminum permeability cup (4 cm inner diameter and 3 cm depth) containing 20 g of Drierite® desiccant. The permeability cups (n=3) were accurately weighed, placed in a humidity chamber at 23°C/80% RH, and periodically reweighed over 96 hours to determine the weight gain. The water vapor transmission rate (WVT) and permeability (P) were calculated using the following equations [13]:

$$WVT = (G/t)/A \qquad \text{(Eq. 6.3)}$$

$$P = \frac{WVT}{S} \times (R_1 - R_2) \times d \qquad \text{(Eq. 6.4)}$$

where G is the weight change, t is the time during which G occurred, A is the test area (cup mouth area), S is the saturation vapor pressure at test temperature, R_1 and R_2 are the relative humidity in the test chamber and inside the cup (0% RH for the desiccant method), respectively, and d is the thickness of the film.

6.2.2.7 Physico-Mechanical Testing

Stress-strain experiments with the sprayed films were performed using an Instron Model 4201 with a 1000 N load cell. Prior to testing, films were cut into 70 mm x 10 mm strips (n=5). The thickness was measured using a Mitutoyo Model ID-C1012EBS digital micrometer (Mitutoyo Corp., JP) and the average of five different measurements along the length of the film was determined. Stress-strain measurements were conducted on the cut films in accordance with ASTM guideline D 882-02 [14] using a gap distance of 50mm, load range of 1N and crosshead speed of 25 mm/min. The elongation of the films was calculated using Bluehill v.2.5 software.

6.2.2.8 Determination of Thermal Properties

The thermal properties of sprayed films were determined using modulated differential scanning calorimetry (MDSC) with a DSC 2920 (TA Instruments, New Castle, DE, USA). Film samples of 5-10 mg were accurately weighed into aluminum pans and then sealed. The samples were analyzed over a range of -20-100°C with a nitrogen flow rate of 40 ml/min, a heating rate of 12°C/min, and a modulation rate of 0.5°C with a period of 40 seconds. The glass transition temperature (Tg) was determined as the midpoint of the transition using Modulated DSC Analysis V 1.1A software.

6.2.2.9 Statistical Analysis

Statistical analysis of in vitro dissolution data was conducted using the f_2 similarity factor treatment described by Shah and associates [15]. Statistical evaluation of the physico-mechanical properties and water vapor permeability of sprayed films was conducted with Minitab Release 14 software using the one-way analysis of variance

(ANOVA) with α=0.05 for a 95% confidence level and Tukey's HSD post hoc test was used to compare the means of each population.

6.3 RESULTS AND DISCUSSION

The lowering of the glass transition temperature (Tg) of a material from plasticization is due to the weakening of inter-polymeric bonds, resulting in an increase in the polymer chain flexibility. Acrylic polymers have been traditionally formulated with citrate esters (triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl tributyl citrate), dibutyl sebacate, and triacetin to lower both the minimum film formation temperature and the Tg of the polymer. However, it has been reported that plasticizer loss during storage from polymeric systems used in sustained release coating applications influenced the physico-mechanical stability of films [16, 17]. Thus, the formulation of a polymeric blend for sustained release applications that did not employ volatile plasticizers, yet still formed coherent films at low processing temperatures, was of interest.

The plasticization of a high Tg material can also be achieved by blending it with a miscible polymer that possesses a lower Tg [11, 12]. It has been reported that two materials have the potential for miscibility if the Hansen solubility parameters have a difference which is ≤ 7 $MPa^{1/2}$ [18]. The Hansen solubility parameters of both Eudragit® NE 30 D and Eudragit® RS 30 D have been calculated at 17.1 $MPa^{1/2}$ [19], which indicated that the two polymers have the potential for miscibility. Equation 6.5, developed by Couchman [20], has been used [12] to predict the Tg of miscible polymer blends, where Tg_{12} is the glass transition temperature of the composite, Tg_1 and w_1 are the Tg and the weight fraction of the lower Tg polymer, respectively, and Tg_2 and w_2 are the Tg and weight fraction of the higher Tg polymer, respectively.

$$Tg_{12} = (Tg_1 \times w_1) + (Tg_2 \times w_2) \qquad \text{(Eq. 6.5)}$$

Modulated differential scanning calorimetry (MDSC) studies on films prepared from Eudragit® NE 30 D and Eudragit® RS 30 D separately showed the Tg to be 12.93°C and 67.03°C, respectively. These values corresponded well with those previously reported in the literature [19]. MDSC revealed that 1:1 and 2:1 blends of Eudragit® NE 30D: Eudragit® RS 30 D were completely miscible at these ratios and showed single transitions of 38.09°C and 23.14°C, respectively. These values were close to the predicted values of 39.5°C for the 1:1 blend and 30°C for the 2:1 blend. Krajacic and Tucker [21] have shown that tablets comprising Eudragit® NE 30 D as a polymeric matrix-forming material would continue to cure in a dissolution medium heated to 37°C if the matrix was incompletely formed. To negate the effect of dissolution media temperature on drug release, formulations composed of a 1:1 ratio of Eudragit® NE 30 D:RS 30 D with a Tg of 38.09°C were selected for further studies.

One method used in previous studies to investigate the physical aging of polymers is by following the water vapor permeability of thin films [5, 9, 10, 17, 22, 23]. The water vapor permeability of sprayed Eudragit® NE 30 D films is shown in Figure 6.1. These films were characterized by very low permeability values and exhibited statistically significant differences between the initial samples and those stored for one month at both 25°C (ANOVA, $p=0.004$) and 40°C (ANOVA, $p=0.001$). Tukey's HSD post hoc analysis (Table 6.1 and Table 6.2) indicated that the permeability at all time points were significantly smaller than the permeability of the films initially tested. Physical aging of these systems was evident due to a densification and continuing coalescence of the low Tg polymer. The permeability of Eudragit® NE 30 D films could be enhanced by blending the polymer with an equal amount of Eudragit® RS 30 D as shown in Figure 6.2. At the initial time point, the water vapor permeability of the blended acrylic polymer film was five times greater than value for films comprising

Eudragit® NE 30 D alone. This was attributed to higher permeability of Eudragit® RS 30 D polymer. Stability studies showed no statistically significant difference in water vapor permeability between films stored at 25°C (ANOVA, p=0.192) or 40°C (ANOVA, p=0.361) at all time points and indicated no change in the permeability of the films when stored at these conditions.

The elongation of the polymeric films has been determined to monitor the physical aging phenomenon [3, 5, 9, 10, 17]. Changes in these parameters are characterized by a relaxation of the polymer toward a state of equilibrium and can be influenced by factors such as the amount of plasticizer in the formulation, the length of curing time, as well as temperature and humidity storage conditions. The effect of time and temperature on the elongation of sprayed films consisting of a 1:1 blend of Eudragit® NE 30 D:RS 30 D are seen in Figure 6.3 and Figure 6.4. For films stored at 25°C for a period of up to one month (Figure 6.3), there was no statistically significant decrease (ANOVA, p=0.690) indicating that the films were physically stable at this temperature. However, films stored at 40°C (Figure 6.4) did exhibit a significant decrease (ANOVA, p=0.001) in elongation over the 1 month testing period. The results for the post hoc Tukey's HSD analysis are shown in Table 6.3 and indicate that the means of elongation at all time points showed a statistically significant decrease in elongation compared to that of films initially tested. While there was no significant change between the means of the one and two week time points, both were found to be significantly different from the four week time point which indicated that further coalescence and entanglement of the polymer chains occurred for films stored at the higher temperature. This observation contradicted the water vapor permeability studies (Figure 6.2), which showed no change in that parameter over the same time period under the same storage conditions and was

attributed to the increased permeability of the polymeric film by the presence of the more permeable Eudragit® RS 30 D polymer.

The release properties of theophylline from Eudragit® NE 30 D coated pellets are shown in Figure 6.5. Coating of the pellets to a 7.5% weight gain with the poorly permeable polymer resulted in less than 20% of the drug being released after 18 hours in pH 7.4 (50 mM phosphate) buffer. When a 1:1 blend of Eudragit® NE 30 D: RS 30 D was applied to the pellets at a 10% weight gain, the drug release rate increased and more than 60% theophylline was released after 18 hours and resulted in a zero-order drug dissolution profile after an initial lag time of 1-2 hours. The increase in drug release could be explained by the difference in permeability of films formed by the polymers. The chemical makeup of Eudragit® RS 30 D includes quaternary ammonium functional groups that undergo hydration and thus promote swelling and permeability of films comprising this material. Eudragit® NE 30 D lacks these functional groups and the drug release rate is controlled by the thickness of the film coating. These findings corresponded well to the difference in permeability of free films studied during the water vapor permeability trials (Figure 6.1 and Figure 6.2).

The stability upon storage of theophylline pellets coated with the blend of acrylic polymers to a 10% weight gain is shown in Figure 6.6 and Figure 6.7. After coating and curing for 18 hours at 60°C, the pellets were placed in aluminum induction sealed HDPE containers with desiccant at storage conditions of 25°C/60% RH and 40°C/75% RH for a period of up to 3 months. Coated pellets stored at the lower temperature (Figure 6.6) were stable during the 3 month period, with an f_2 similarity factor of 78 between the initial dosage forms and those stored for 3 months. In contrast, those pellets stored at the higher temperature (Figure 6.7) exhibited a decrease in drug release rate during this time period and the f_2 similarity factor for the drug release rate between the initial dosage

forms and those stored for three months was 53. Though no change in water vapor permeability was seen for sprayed films stored at 40°C, the difference between this parameter and dissolution performance was confirmed by the results of the physico-mechanical properties of the sprayed films, in which there was a significant decrease in elongation for these samples (Figure 6.4). The films were stored at a temperature which was above the Tg of the polymeric composite and dissolution was performed at a temperature below the Tg. At this point, the molecular mobility of the polymer chains is high and continuing coalescence and densification of the polymer occurred during storage. During dissolution, hydrodynamic effects are exerted on the coated pellets, including diffusion of water to the core. The increase in core volume due to osmotic effects causes the film to expand. Increased coalescence of the polymer during storage at temperatures above the Tg significantly affected the ability of the film to expand during dissolution and the reduction in drug release rate was a direct result of the instability in the elasticity parameter of the film.

6.4 CONCLUSIONS

The combination of the miscible polymers Eudragit® NE and Eudragit® RS 30 D allowed film formation without the requirement of a plasticizer in the formulation. Films containing a 1:1 blend of Eudragit® NE 30 D:RS 30 D possessed a glass transition temperature that was higher than those films consisting of a 2:1 blend and corresponded well to predicted values. Sprayed films composed of Eudragit® NE 30 D:RS 30 D (1:1) and theophylline pellets coated with the same formulation possessed higher water vapor permeability values and drug release rates, respectively, when compared to Eudragit® NE 30 D sprayed films and film-coated dosage forms. This was attributed to the quaternary ammonium groups present in Eudragit® RS 30 D which increased the swellability and permeability of the film. Theophylline pellets coated with a blend of Eudragit® NE 30

D:RS 30 D (1:1) demonstrated a decrease in drug release rate when stored at 40°C/75% RH in aluminum induction sealed HDPE containers. The release properties of coated pellets could be correlated to instabilities in the physico-mechanical properties of sprayed films, which showed a decrease in percent elongation during a time period of 4 weeks when stored at 40°C. This reduced flexibility of the film coating during dissolution was due to increased coalescence and interdiffusion of the polymer chains when stored at temperatures above the Tg of the polymeric blend. However, when the same pellets were stored at 25°C/60% RH (below the glass transition temperature of the blend), the mechanical properties of the films were conserved and no change in drug release rate were observed over a 3 month period. The stability of Eudragit® NE 30 D films could be successfully enhanced by the addition of Eudragit® RS 30 D to the coating formulation.

6.5 REFERENCES

1. Amighi, K. and A.J. Moës. Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit® RS 30 D film-coated sustained-release theophylline pellets. European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42** (1): p. 29-35.

2. Amighi, K. and A.J. Moës. Influence of curing conditions on the drug release rate from Eudragit® NE 30 D film coated sustained-release theophylline pellets. S.T.P. Pharma Sci, 1997. **7** (2): p. 141-147.

3. Gutierrez-Rocca, J.C. and J.W. McGinity. Influence of Physical Aging on the Physical-Mechanical Properties of Acrylic Resin Films Cast from Aqueous Dispersions and Organic Solutions. Drug Dev. Ind. Pharm., 1993. **19** (3): p. 315-332.

4. Wu, C.B. and J.W. McGinity. Influence of relative humidity on the mechanical and drug release properties of theophylline pellets coated with an acrylic polymer containing methylparaben as a non-traditional plasticizer. European Journal of Pharmaceutics and Biopharmaceutics, 2000. **50** (2): p. 277-284.

5. Zheng, W., D. Sauer, and J.W. McGinity. Influence of hydroxyethylcellulose on the drug release properties of theophylline pellets coated with Eudragit® RS 30 D. European Journal of Pharmaceutics and Biopharmaceutics, 2005. **59** (1): p. 147-154.

6. Struik, L.C.E. *Chapter 1 - Scope of the Work*, in *Physical Aging in Amorphous Polymers and Other Materials*, L.C.E. Struik, Editor. 1978, Elsevier Scientific Publishing Company: New York. p. 1.

7. Iyer, U., W.-H. Hong, N. Das, and I. Ghebre-Sellaissie. Comparative evaluation of three organic solvent and dispersion-based ethylcellulose coating formulations. Pharm. Tech., 1990. **14** (9): p. 68-86.

8. Maejima, T. and J.W. McGinity. Influence of film additives on stabilizing drug release rates from pellets coated with acrylic polymers. Pharmaceutical Development and Technology, 2001. **6** (2): p. 211-221.

9. Kucera, S.A., N.H. Shah, A.W. Malick, M.A. Infeld, and J.W. McGinity. The Use of Proteins to Minimize the Physical Aging of Eudragit® Sustained Release Films. Drug Development and Industrial Pharmacy, 2007. **33** (7): p. 717-726.

10. Kucera, S.A., D. Stimpel, N.H. Shah, A.W. Malick, M.H. infeld, and J.W. McGinity. Influence of Fumed Silicon Dioxide on the Stabilization of Eudragit® RS/RL 30 D Film-Coated Theophylline Pellets. Pharm. Dev. Tech., 2008. **In Press**

11. Wu, C. and J.W. McGinity. Influence of an Enteric Polymer on Drug Release Rates of Theophylline from Pellets Coated with Eudragit® RS 30 D. Pharm. Dev. Tech., 2003. **8** (1): p. 103-110.

12. Zheng, W. and J.W. McGinity. Influence of Eudragit® NE 30 D Blended with Eudragit® L 30 D-55 on the Release of Phenylpropanolamine Hydrochloride from Coated Pellets. Drug Development and Industrial Pharmacy, 2003. **29** (3): p. 357-366.

13. ASTM. ASTM E 96/E 96 M-05: Standard Test Methods for Water Vapor Transmission of Materials. American Society for Testing Materials, 2005

14. ASTM. ASTM D 882-02 : Standard Test Method for Tensile Properties of Thin Plastic Sheeting. American Society for Testing Materials, 2002

15. Shah, V.P., Y. Tsong, P. Sathe, and J.-P. Liu. *In Vitro* Dissolution Profile Comparison - Statistics and Analysis of the Similariry Factor, f_2. Pharmaceutical Research, 1998. **15** (6): p. 889-896.

16. Gutierrez-Rocca, J.C. and J.W. McGinity. Influence of Water-Soluble and Insoluble Plasticizers on the Physical and Mechanical-Properties of Acrylic Resin Copolymers. International Journal of Pharmaceutics, 1994. **103** (3): p. 293-301.

17. Heng, P.W.S., L.W. Chan, and K.T. Ong. Influence of Storage Conditions and Type of Plasticizers on Ethylcellulose and Acrylate Films Formed from Aqueous Dispersions. J Pharm Pharmaceut Sci, 2003. **6** (3): p. 334-344.

18. Forster, A., J. Hempenstall, I. Tucker, and T. Rades. Selection of excipients for melt extrusion with two poorly water-soluble drugs by solubility parameter calculation and thermal analysis. International Journal of Pharmaceutics, 2001. **226** (1-2): p. 147-161.

19. Degussa. Innovative formulations from melt extrusions. Degussa GmbH Pharma Polymers, Darmstadt, Germany, 2007

20. Couchman, P.R. Compositional variation of glass transition temperature. 2. Application of the thermodynamics theory to compatible polymer blends. Macromolecules, 1978. **11** (6): p. 1156-1161.

21. Krajacic, A. and I.G. Tucker. Matrix formation in sustained release tablets: possible mechanism of dose dumping. International Journal of Pharmaceutics, 2003. **251** (1-2): p. 67-78.

22. Guo, J.-H. A Theoretical and Experimental Study of the Additive Effects of Physical Aging and Antiplasticization on the Water Permeability of Polymer Film Coatings. Journal of Pharmaceutical Sciences, 1994. **83** (3): p. 447-449.

23. Heinämäki, J.T., V.-M. Lehtola, P. Nikupaavo, and J.K. Yliruusi. The mechanical and moisture permeability properties of aqueous-based hydroxypropyl methylcellulose coating systems plasticized with polyethylene glycol. International Journal of Pharmaceutics, 1994. **112** (2): p. 191-196.

6.6 TABLES

	Initial	1 Week	2 week
1 Week	X		
2 Weeks	X	O	
4 Weeks	X	O	O

Table 6.1 Pair-wise comparisons performed by Tukey's HSD post hoc analysis with a 95% simultaneous confidence interval of the water vapor permeability of Eudragit® NE 30 D sprayed films stored at 25°C for a period of up to 4 weeks (X, significant difference; O, no significant difference).

	Initial	1 Week	2 Week
1 Week	X		
2 Weeks	X	O	
4 Weeks	X	O	O

Table 6.2 Pair-wise comparisons performed by Tukey's HSD post hoc analysis with a 95% simultaneous confidence interval of the water vapor permeability of Eudragit® NE 30 D sprayed films stored at 40°C for a period of up to 4 weeks (X, significant difference; O, no significant difference).

	Initial	1 Week	2 Weeks
1 Week	X		
2 Weeks	X	O	
4 Weeks	X	X	X

Table 6.3 Pair-wise comparisons performed by Tukey's HSD post hoc analysis with a 95% simultaneous confidence interval of the percent elongation of Eudragit® NE 30 D:Eudragit® RS 30 D (1:1) sprayed films stored at 40°C for a period of up to 4 weeks (X, significant difference; O, no significant difference).

6.7 FIGURES

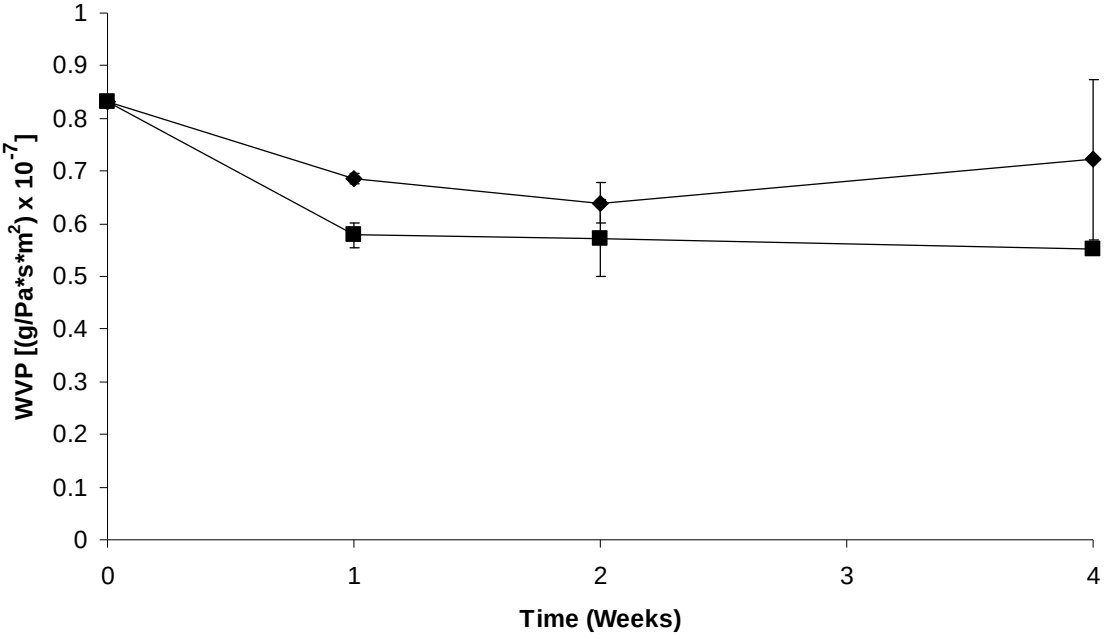


Figure 6.1 The effect of temperature and time on the water vapor permeability of Eudragit® NE 30 D sprayed films (◆, 25°C; ■, 40°C) (tested at 25°C/80% RH, *n*=3).

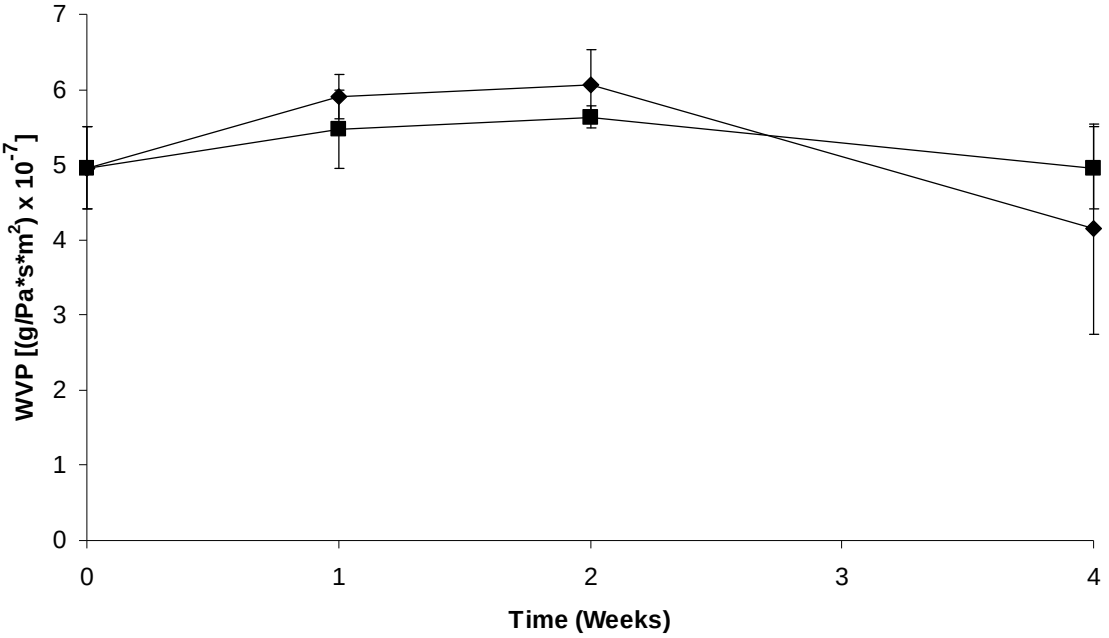


Figure 6.2 The effect of temperature and time on the water vapor permeability of Eudragit® NE 30 D:Eudragit® RS 30 D (1:1) sprayed films (◆, 25°C; ■, 40°C) (tested at 25°C/80% RH, *n*=3).

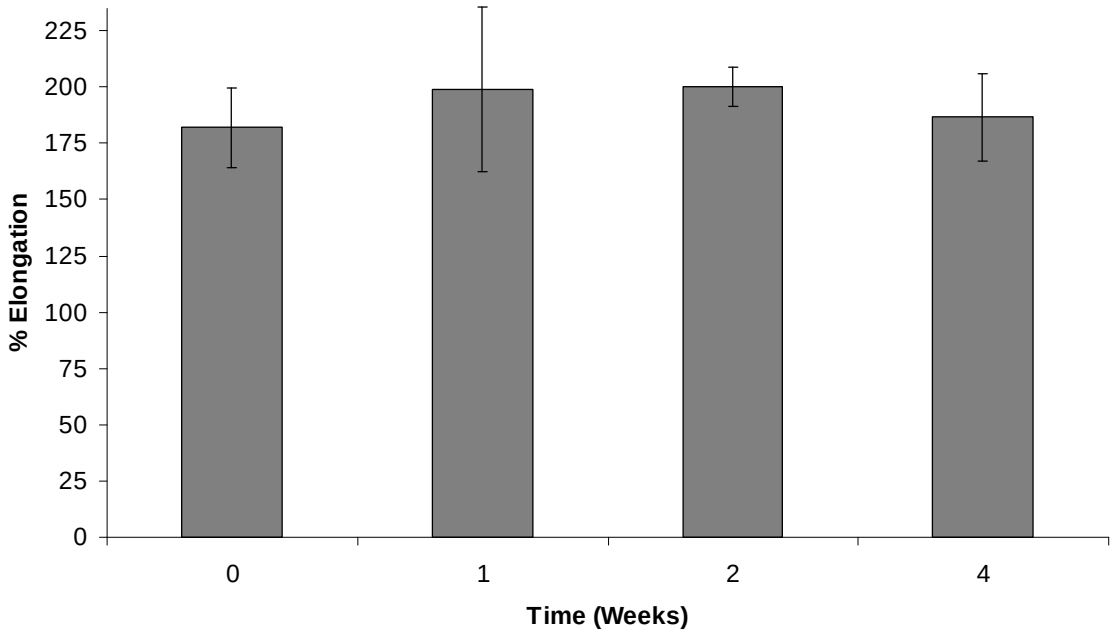


Figure 6.3 The influence of temperature and time on the percent elongation properties of Eudragit® NE 30 D:Eudragit® RS 30 D (1:1) sprayed films stored at 25°C (*n*=*5*).

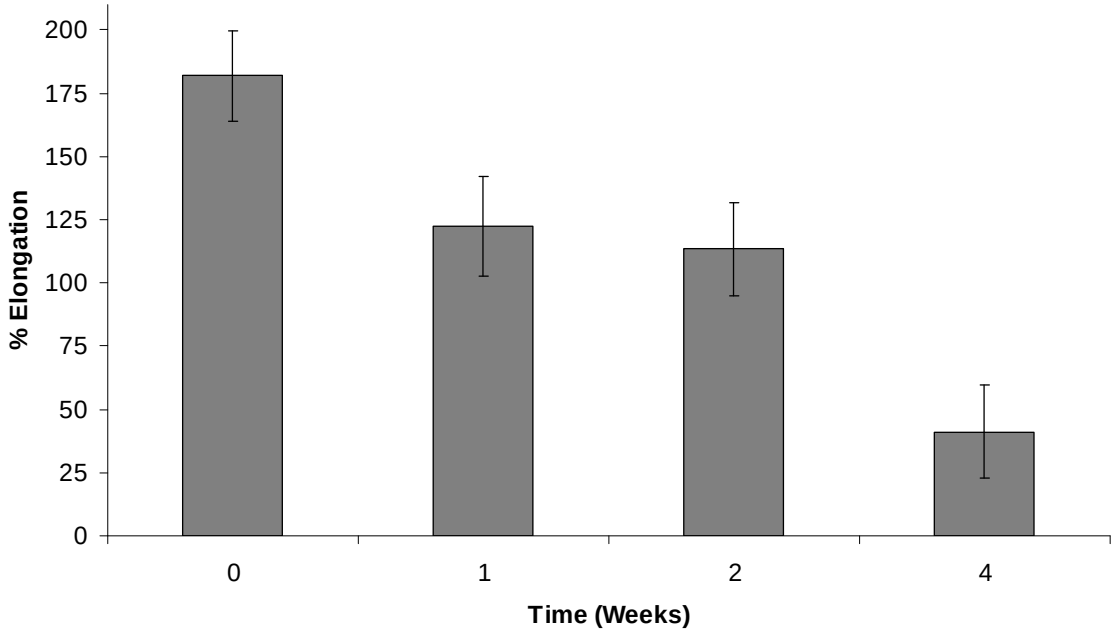


Figure 6.4 The influence temperature and time on the percent elongation properties of Eudragit® NE 30 D:Eudragit® RS 30 D (1:1) sprayed films stored at 40°C (*n*=*5*).

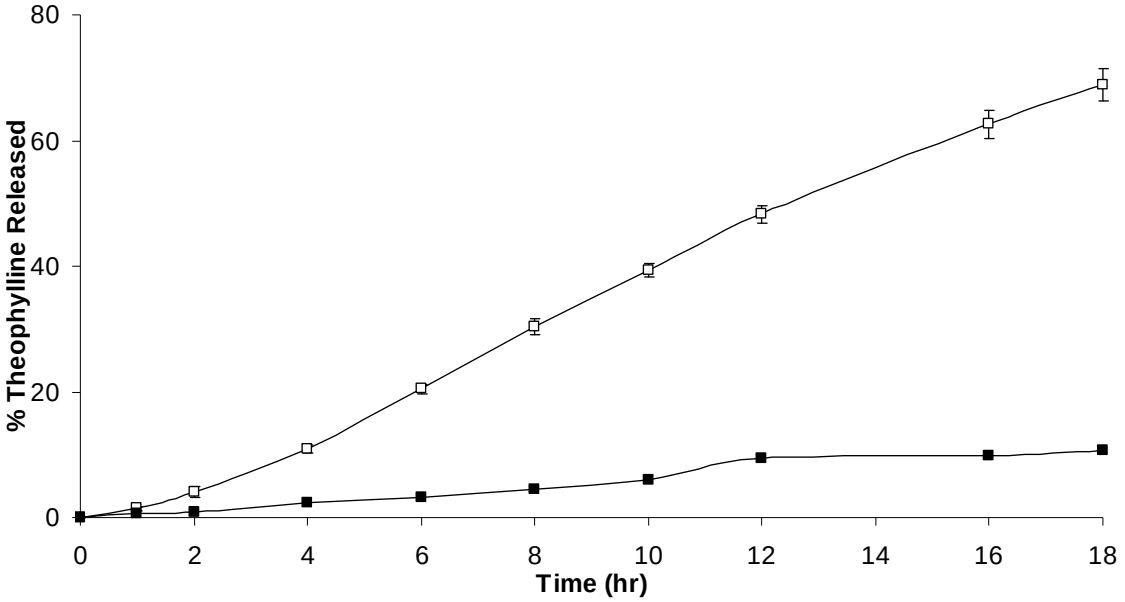


Figure 6.5 The influence of the addition of Eudragit® RS 30 D on the release of theophylline from coated pellets (□, Eudragit® NE 30 D:Eudragit® RS 30 D (1:1), 50% Imperial® 500 talc, 10% W.G.; ■, Eudragit® NE 30 D, 50% Imperial® 500 talc, 7.5% W.G.) (USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, *n*=3).

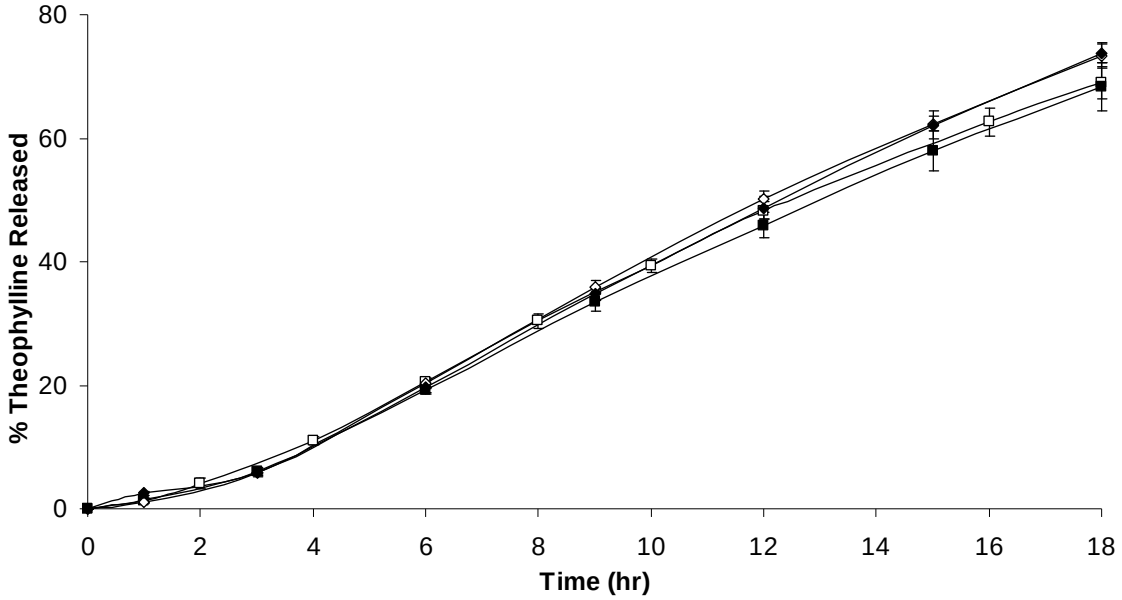


Figure 6.6 The influence of storage time on the release of theophylline (30 mg) from pellets coated with Eudragit® NE 30 D:Eudragit® RS 30 D (1:1) and 50% Imperial® 500 talc coated to a 10% weight gain and stored in sealed HDPE containers with desiccant at 25°C/60% RH (□, initial; ■, 2 week; ◇, 1 month; ◆, 3 month)(USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, *n*=3).

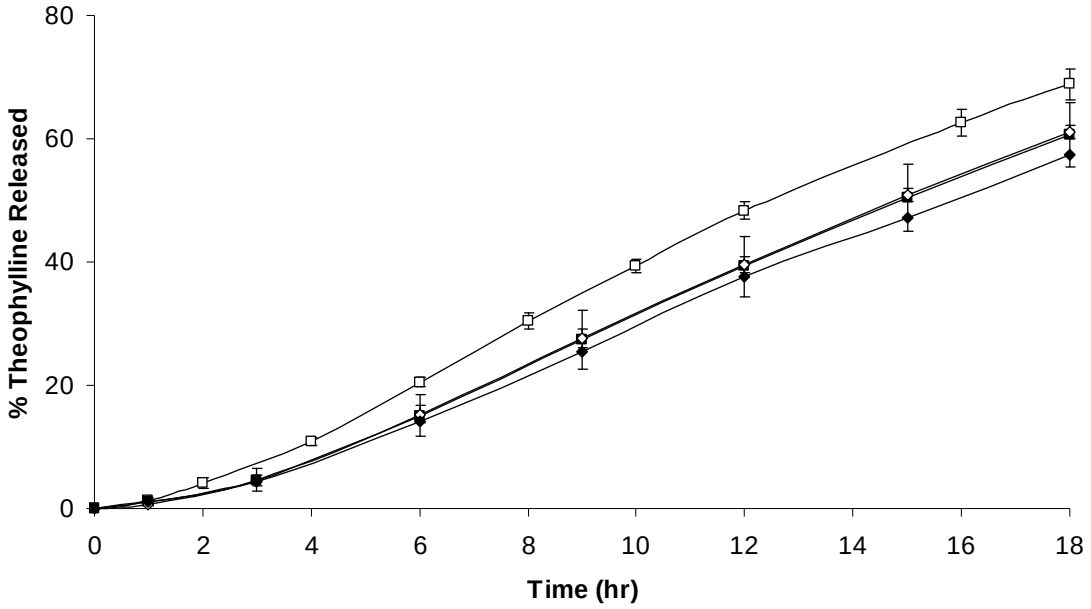


Figure 6.7 The influence of storage time on the release of theophylline (30 mg) from pellets coated with Eudragit® NE 30 D:Eudragit® RS 30 D (1:1) and 50% Imperial® 500 talc coated to a 10% weight gain and stored in sealed HDPE containers with desiccant at 40°C/75% RH (□, initial; ■, 2 week; ◇, 1 month; ◆, 3 month)(USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, *n*=3).

Chapter 7: Conclusions

7.1 The Use of Proteins to Minimize the Physical Aging of Eudragit® Sustained Release Films

The influence of the addition of bovine serum albumin and Type B gelatin on the physical aging and physico-mechanical properties of 95:5 blends of Eudragit® RS30 D:RL 30 D was investigated. Coating formulations of the acrylic dispersions plasticized with 15% TEC and containing 10% Type B gelatin were shown to enhance the theophylline release rate from film-coated pellets, which was attributed to the formation of gel domains in which the drug was able diffuse through easily. Adjustment of the acrylic dispersion pH to more acidic values did not impact drug release. The zeta potential of the blend was maintained due to the isoelectric point of the gelatin being above that of the acrylic dispersion. While the physico-mechanical parameters of sprayed films indicated aging in these systems, the water vapor permeability values remained constant during a one month period when stored in open containers under conditions of 40°C/75% RH. It was shown that the addition of Type B gelatin to Eudragit® RS/RL 30 D dispersions stabilized the drug release rate from coated theophylline pellets stored in both open and closed containers at 40°C/75% RH over a period of 3 months. The mechanism of stabilization in these films was attributed to the maintenance in permeability of the films. On the other hand, the inclusion of 10% bovine serum albumin to the coating dispersions exhibited an increase in particle size and a decrease in colloidal electrostatic charge due to electrostatic interactions between the positively charged quaternary ammonium groups of the polymer and the protein which was negatively charged at the native dispersion pH. Significant decreases in the water vapor permeability and changes in the physico-mechanical properties of sprayed films

indicated significant aging in these systems which corresponded to the decrease in drug release rate observed over a period of six months at 40°C/75% RH in open containers. Dissolution media was found to influence the surface charge of albumin in the acrylic films and the protein was released in 0.1 N HCl but remained in the films at pH 7.4, indicating that the drug release rate would not be affected by the formation of pores during dissolution. Physically stable films were formed by adjusting the pH of the acrylic dispersion to 2.5, below the isoelectric point of albumin, and the stabilization in drug release rate from theophylline pellets coated with this formulation and stored at 40°C/75% RH and 25°C/60% RH was attributed to like-like repulsive forces between the two positively charged components.

7.2 INFLUENCE OF FUMED SILICON DIOXIDE ON THE STABILIZATION OF EUDRAGIT® RS/RL 30 D FILM-COATED THEOPHYLLINE PELLETS

The effects of silicon dioxide on the drug release rate and physical stability of Eudragit® RS/RL 30 D films were the aims of this study. Silicon dioxide with particle sizes in the colloidal range (Cab-O-Sil® M-5P and Aerosil® 200 VV) exhibited enhanced incorporation of the excipient into the polymeric film. Pellets coated with these formulations displayed drug release rates and water vapor permeability values that were significantly lower than those pellets coated with the larger particle size Aeroperl® 300, which was found to be present in the film in large agglomerates. Theophylline pellets coated to a 20% weight gain of Eudragit® RS 30 D, 15% TEC, and 30% Aeroperl® 300 exhibited zero-order release kinetics and were stable during a storage period of 2 months at 25°C/60% RH in sealed HDPE containers. The mechanism of stability was due to the water vapor permeability of sprayed films, which showed no change during storage at 25°C. Changes in the theophylline release rate of pellets coated with a 90:10 blend of Eudragit® RS 30 D:RL 30 D plasticized with 15% TEC and containing either Cab-O-Sil®

M-5P or Aerosil® 200 VV coincided with small changes in the water vapor permeability of cast films which showed slight statistical decreases and increases, respectively.

7.3 THE INFLUENCE OF ETHYLCELLULOSE POLYMERS ON THE PHYSICAL STABILITY OF THEOPHYLLINE PELLETS COATED WITH EUDRAGIT® NE 30 D

The particle size of Ethocel® S4 was found to influence the release of theophylline pellets coated with Eudragit® NE 30 D in that those formulations containing larger particle size ethylcellulose powder exhibited a decrease in drug release compared to smaller particle size ethylcellulose. The Hansen solubility parameters of the acrylic and cellulosic polymers indicated possible miscibility between the two materials; however, thermal data showed that the miscible phase was only a small fraction of the total composite and the films were largely composed of ethylcellulose powdered dispersed in Eudragit® NE 30 D. The addition of Ethocel® 7 FP to the coating dispersion increased the permeability of the films and accelerated the rate at which theophylline was released from the coated pellets. The formation of pores and channels in these films during dissolution was attributed to the loss of ethylcellulose from the film, which occurred during the swelling of the polymer during dissolution. Theophylline pellets coated with a 2:1 blend of Eudragit® NE 30 D:Ethocel® 7 FP exhibited a stable drug release rate over the course of 3 months at both 25°C/60% RH and 40°C/75% RH when stored in aluminum induction sealed HDPE containers. The stabilization in drug release rate was attributed to constant water vapor permeability values and physico-mechanical properties of the sprayed films. The presence of Ethocel® 7 FP in the Eudragit® NE 30 D films prevented the densification and further coalescence of the polymer at temperatures well above the glass transition temperature of the acrylic polymer.

7.4 INFLUENCE OF AN ACRYLIC POLYMER BLEND ON THE PHYSICAL STABILITY OF FILM-COATED THEOPHYLLINE PELLETS

The requirement of a plasticizer to aid in film formation was not necessary when Eudragit® RS 30 D and Eudragit® NE 30 D were blended. The glass transition temperature of the blend was affected by the ratio in which the polymers were present and were found to be close to predicted values. Sprayed films consisting of a 1:1 blend of Eudragit® NE 30 D:Eudragit® RS 30 D possessed water vapor permeability values that were five times those values of Eudragit® NE 30 D alone and was due to the presence of the quaternary ammonium groups in the chemical structure of Eudragit® RS 30 D. Theophylline pellets stored at 40°C/75% RH in aluminum induction sealed HDPE containers exhibited a decrease in drug release rate over a 3 month period of time due to a further densification of the acrylic film when stored above the glass transition temperature of the polymeric blend. On the other hand, those pellets stored in aluminum induction sealed HDPE containers with desiccant at 25°C/60% RH exhibited excellent stability due to storage at temperatures below the Tg of the polymer. The decrease in drug release rate was attributed to instabilities in the mechanical properties of the sprayed polymeric films, which showed a reduction in elongation for films stored at the higher temperature and was due to increased coalescence and interdiffusion of the polymer chains at storage conditions above the Tg of the polymer blend.

Bibliography

Ageeva, M. G. (1970). Moisture-resistant film coatings for orally administered medicinal forms. *Pharmaceutical Chemistry Journal*, 4 (6), 342-346.

Amighi, K. & Moës, A. J. (1996). Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit® RS 30 D film-coated sustained-release theophylline pellets. *European Journal of Pharmaceutics and Biopharmaceutics*, 42 (1), 29-35.

Amighi, K. & Moës, A. J. (1997). Influence of curing conditions on the drug release rate from Eudragit® NE 30 D film coated sustained-release theophylline pellets. *S.T.P. Pharma Sci*, 7 (2), 141-147.

Anderson, W. & Abdel-Aziz, S. A. M. (1976). Ageing Effects in Cast Acrylate-Methacrylate Film. *J. Pharm. Pharmacol.*, 28 (Suppl: 22P),

Arno, E. A., Anand, P., Bhaskar, K., Ramachandran, S., Saravanan, M. & Vinod, R. (2002). Eudragit® NE 30 D Based Metformin/Gliclazide Extended Release Tablets: Formulation, Characterisation, and *in Vitro* Release Studies. *Chem Pharm Bull*, 50 1495-1498.

ASTM (2000). ASTM E 96-00: Standard Test Methods for Water Vapor Transmission of Materials. American Society for Testing Materials,

ASTM (2001). ASTM D 2990-01: Standard Test Methods for Tensile, Compressive, and Flexuraly Creep and Creep-Rupture of Plastics. American Society for Testing Materials,

ASTM (2002). ASTM D 882-02 : Standard Test Method for Tensile Properties of Thin Plastic Sheeting. American Society for Testing Materials,

ASTM (2005). ASTM E 96/E 96 M-05: Standard Test Methods for Water Vapor Transmission of Materials. American Society for Testing Materials,

Bajdik, J., Pintye-Hodi, K., Planinsek, O., Tuske, Z., Tasic, L., Regdon, G., Srcic, S. & Eros, I. (2004). Surface Treatment of Indomethacin Agglomerates with Eudragit. *Drug Development and Industrial Pharmacy*, 30 (4), 381-388.

Bajdik, J., Pintye-Hodi, K., Regdon, G. J., Fazekas, P., Szabo-Revesz, P. & Eros, I. (2003). The effect of storage on the behaviour of Eudragit® NE free film. *Journal of Thermal Analysis and Calorimetry*, 73 (2), 607-613.

Barbero, E. J. & Ford, K. J. (2004). Equivalent Time Temperature Model for Physical Aging and Temperature Effects on Polymer Creep and Relaxation. *Journal of Engineering Materials and Technology*, 126 (4), 413-419.

Bigg, D. M. (1996). A review of positron annihilation lifetime spectroscopy as applied to the physical aging of polymers. *Polymer Engineering & Science*, 36 (6), 737-743.

Billa, N., Yuen, K.-H. & Peh, K.-K. (1998). Diclofenac release from Eudragit-containing matrices and effects of thermal treatment. *Drug Dev. Ind. Pharm.*, 24 (1), 45-50.

Cangialosi, D., Schut, H., van Veen, A. & Picken, S. J. (2003). Positron Annihilation Lifetime Spectroscopy for Measuring Free Volume During Physical Aging of Polycarbonate. *Macromolecules*, 36 (1), 142-147.

Chan, A., Coppens, K., Hall, M., He, V., Jog, P., Larsen, P., Koblinksi, B., Read, M., Rothe, D., Somasi, S. & Shrestha, U. (2006). Solubility parameters as a tool to predict API morphology in hot melt extruded (HME) formulations containing ethycellulose, hypromellose, and polyethylene oxide. 2006 American Association of Pharmaceutical Scientists Annual Meeting and Exposition, San Antonio, TX, 29 October/ 2 November 2006.

Chang, G.-W., Jamieson, A. M., Yu, Z. & McGervey, J. D. (1997). Physical aging in the mechanical properties of miscible polymer blends. *Journal of Applied Polymer Science*, 63 (4), 483-496.

Chowhan, Z. T., Amaro, A. A. & Chi, L.-H. (1982). Comparative Evaluations of Aqueous Film Coated Tablet Formulations by High Humidity Aging. *Drug Dev. Ind. Pharm.*, 8 (5), 713-737.

Couchman, P. R. (1978). Compositional variation of glass transition temperature. 2. Application of the thermodynamics theory to compatible polymer blends. *Macromolecules*, 11 (6), 1156-1161.

Dai, C.-A. & Liu, M.-W. (2006). The effect of crystallinity and aging enthalpy on the mechanical properties of gelatin films. *Materials Science and Engineering: A Mechanical Behaviour of Micro- and Nano-scale Systems*, 423 (1-2), 121-127.

Degussa (2007). Innovative formulations from melt extrusions. Degussa GmbH Pharma Polymers, Darmstadt, Germany

Dow (2005). Ethocel®: Ethylcellulose polymers technical handbook. Dow Cellulosics, Midland, MI, USA

Drozdov, A. D. (1999). A Constitutive Model for Physical Ageing in Amorphous Glassy Polymers. *Modelling Simul. Mater. Sci. Eng*, 7 (6), 1045-1060.

Drozdov, A. D. (1999). Physical aging in amorphous polymers far below the glass transition temperature. *Computational Materials Science*, 15 (4), 422-434.

Felton, L. A. & McGinity, J. W. (1999). Influence of pigment concentration and particle size on adhesion of an acrylic resin copolymer to tablet compacts. *Drug Development and Industrial Pharmacy*, 25 (5), 597-604.

Forster, A., Hempenstall, J., Tucker, I. & Rades, T. (2001). Selection of excipients for melt extrusion with two poorly water-soluble drugs by solubility parameter calculation and thermal analysis. *International Journal of Pharmaceutics*, 226 (1-2), 147-161.

Frisbee, S. E., Mehta, K. A. & McGinity, J. W. (2002). Processing Factors that Influence the In Vitro and Performance of Film-Coated Drug Delivery Systems. *Drug Delivery Technology*, 21 (1), 72-76.

Gordon, M. & Taylor, J. S. (1952). Ideal copolymers and the second-order transitions of synthetic rubbers. I. Noncrystalline copolymers. *Journal of Applied Chemistry*, 2 493-500.

Greiner, R. & Schwarzl, F. R. (1989). Volume relaxation and physical aging of amorphous polymers I. Theory of volume relaxation after single temperature jumps. *Colloid & Polymer Science*, 267 (1), 39-47.

Guo, J.-H. (1994). A Theoretical and Experimental Study of the Additive Effects of Physical Aging and Antiplasticization on the Water Permeability of Polymer Film Coatings. *Journal of Pharmaceutical Sciences*, 83 (3), 447-449.

Guo, J.-H. (1999). Aging processes in pharmaceutical polymers. *Pharm. Sci. Technol. Today*, 2 (12), 478-483.

Guo, J.-H., Robertson, R. E. & Amidon, G. L. (1991). Influence of Physical Aging on Mechanical Properties of Polymer Free Films: The Prediction of Long-Term Aging Effects on the Water Permeability and Dissolution Rate of Polymer Film-Coated Tablets. *Pharmaceutical Research*, 8 (12), 1500-1504.

Guo, J.-H., Robertson, R. E. & Amidon, G. L. (1993). An Investigation into the Mechanical and Transport Properties of Aqueous Latex Films: A New Hypothesis for the Film-Forming Mechanism of Aqueous Dispersion System. *Pharmaceutical Research*, 10 (3), 405-410.

Gutierrez-Rocca, J. C. & McGinity, J. W. (1993). Influence of Physical Aging on the Physical-Mechanical Properties of Acrylic Resin Films Cast from Aqueous Dispersions and Organic Solutions. *Drug Dev. Ind. Pharm.*, 19 (3), 315-332.

Gutierrez-Rocca, J. C. & McGinity, J. W. (1994). Influence of Water-Soluble and Insoluble Plasticizers on the Physical and Mechanical-Properties of Acrylic Resin Copolymers. *International Journal of Pharmaceutics*, 103 (3), 293-301.

Heinämäki, J. T., Lehtola, V.-M., Nikupaavo, P. & Yliruusi, J. K. (1994). The mechanical and moisture permeability properties of aqueous-based hydroxypropyl methylcellulose coating systems plasticized with polyethylene glycol. *International Journal of Pharmaceutics*, 112 (2), 191-196.

Heng, P. W. S., Chan, L. W. & Ong, K. T. (2003). Influence of Storage Conditions and Type of Plasticizers on Ethylcellulose and Acrylate Films Formed from Aqueous Dispersions. *J Pharm Pharmaceut Sci*, 6 (3), 334-344.

Hu, L.-D., Liu, Y., Tang, X. & Zhang, Q. (2006). Preparation and in vitro/in vivo evaluation of sustained-release metformin hydrochloride pellets. *European Journal of Pharmaceutics and Biopharmaceutics*, 64 (2), 185-192.

Huang, Y. & Paul, D. R. (2004). Experimental Methods for Tracking Physical Aging of Thin Glassy Polymer Films by Gas Permeation. *J Membrane Sci*, 244 (1-2), 167-178.

Huang, Y. & Paul, D. R. (2004). Physical aging of thin glassy polymer films monitored by gas permeability. *Polymer*, 45 (25), 8377-8393.

Huang, Y. & Paul, D. R. (2005). Effect of Temperature on Physical Aging of Thin Glassy Polymer Films. *Macromolecules*, 38 (24), 10148-10154.

Huang, Y. & Paul, D. R. (2006). Physical Aging of Thin Glassy Polymer Films Monitored by Optical Properties. *Macromolecules*, 39 (4), 1554-1559.

Huang, Y., Wang, X. & Paul, D. R. (2006). Physical aging of thin glassy polymer films: Free volume interpretation. *Journal of Membrane Science*, 277 (1-2), 219-229.

Hutchinson, J. M. (1995). Physical aging of polymers. *Progress in Polymer Science*, 20 (4), 703-760.

Iyer, U., Hong, W.-H., Das, N. & Ghebre-Sellaissie, I. (1990). Comparative evaluation of three organic solvent and dispersion-based ethylcellulose coating formulations. *Pharm. Tech.*, 14 (9), 68-86.

Kawana, S. & Jones, R. A. L. (2003). Effect of physical ageing in thin glassy polymer films. *The European Physical Journal E - Soft Matter*, V10 (3), 223-230.

Khamanga, S. M. & Walker, R. B. (2006). Evaluation of Rate of Swelling and Erosion of Verapamil (VRP) Sustained-Release Matrix Tablets. *Drug Development and Industrial Pharmacy*, 32 (10), 1139-1148.

Kobayashi, Y., Zheng, W., Meyer, E. F., McGervey, J. D., Jamieson, A. M. & Simha, R. (1989). Free volume and physical aging of poly(vinyl acetate) studied by positron annihilation. *Macromolecules*, 22 (5), 2302-2306.

Krajacic, A. & Tucker, I. G. (2003). Matrix formation in sustained release tablets: possible mechanism of dose dumping. *International Journal of Pharmaceutics*, 251 (1-2), 67-78.

Kucera, S. A., Shah, N. H., Malick, A. W., Infeld, M. A. & McGinity, J. W. (2007). The Use of Proteins to Minimize the Physical Aging of Eudragit® Sustained Release Films. *Drug Development and Industrial Pharmacy*, 33 (7), 717-726.

Kucera, S. A., Stimpel, D., Shah, N. H., Malick, A. W., infeld, M. H. & McGinity, J. W. (2008). Influence of Fumed Silicon Dioxide on the Stabilization of Eudragit® RS/RL 30 D Film-Coated Theophylline Pellets. *Pharm. Dev. Tech.*, In Press

Lin, A. Y. & Augsburger, L. L. (2001). Study of Crystallization of Endogenous Surfactant in Eudragit NE 30 D-Free Films and Its Influence on Drug-Release Properties of Controlled-Release Diphenhydramine HCl Pellets Coated with Eudragit NE 30 D. *AAPS PharmSci.*, 3 (2),

Lin, A. Y., Muhammad, N. A., Pope, D. & Augsburger, L. L. (2003). A Study on the Effects of Curing and Storage Conditions on Controlled Release Diphenhydramine HCl Pellets Coated with Eudragit® NE 30 D. *Pharm. Dev. Tech.*, 8 (3), 277-287.

Lin, F. & Meier, D. J. (1995). A Study of Latex Film Formation by Atomic Force Microscopy. 1. A Comparison of Wet and Dry Conditions. *Langmuir*, 11 (7), 2726-2733.

Lippold, B. C. & Pages, R. M. (2001). Film Formation, Reproducibility of Production and Curing with Respect to Release Stability of Functional Coatings from Aqueous Polymer Dispersions. *Pharmazie*, 56 (1), 5-17.

Maejima, T. & McGinity, J. W. (2001). Influence of film additives on stabilizing drug release rates from pellets coated with acrylic polymers. *Pharmaceutical Development and Technology*, 6 (2), 211-221.

Matsumoto, D. S. (1988). Time-temperature superposition and physical aging in amorphous polymers. *Polymer Engineering & Science*, 28 (20), 1313-1317.

Maul, K. A. & Schmidt, P. C. (1995). Influence of different-shaped pigments on bisacodyl release from Eudragit L 30 D. *International Journal of Pharmaceutics*, 118 (1), 103-112.

McCaig, M. S. & Paul, D. R. (2000). Effect of film thickness on the changes in gas permeability of a glassy polyarylate due to physical agingPart I. Experimental observations. *Polymer*, 41 (2), 629-637.

Montes, H., Viasnoff, V., Jurine, S. & Lequeux, F. (2006). Ageing in glassy polymers under various thermal histories. *Journal of Statistical Mechanics: Theory and Experiment*, (March), P03003.

Nyamweya, N., Mehta, K. A. & Hoag, S. W. (2001). Characterization of the interactions between polymethacrylate-based aqueous polymeric dispersions and aluminum lakes. *J. Pharm. Sci.*, 90 (12), 1937-1947.

Nyamweya, N., Mehta, K. A. & Hoag, S. W. (2001). Film coating with aqueous latex dispersions: general considerations for formulating with pigments. *Pharm. Tech.*, (Yearbook), 8, 10-12, 26.

Obara, S. & McGinity, J. W. (1994). Properties of Free Films Prepared from Aqueous Polymers by a Spraying Technique. *Pharmaceutical Research*, 11 (11), 1562-1567.

Ojoe, E., Miyauchi, E. M., Viviani, T. C. & Consiglieri, V. O. (2005). Formulation and in vitro evaluation of theophylline-Eudragit® sustained-release tablets. *Rev. Bras. Cienc. Farm.*, 41 377-384.

Okhamafe, A. O. & York, P. (1984). Effect of solids-polymer interactions on the properties of some aqueous-based tablet film coating formulations. II. Mechanical characteristics. *International Journal of Pharmaceutics*, 22 273-281.

Okhamafe, A. O. & York, P. (1985). Relationship between stress, interaction and the mechanical properties of some pigmented tablet coating films. *Drug Development and Industrial Pharmacy*, 11 (1), 131-146.

Omari, D. M., Sallam, A., Abd-Elbary, A. & El-Samaligy, M. (2004). Lactic acid-induced modifications in films of Eudragit® RL and RS aqueous dispersions. *International Journal of Pharmaceutics*, 274 (1-2), 85-96.

Parker, J. W., Peck, G. E. & Banker, G. S. (1974). Effects of solids-loading on moisture permeability coefficients of free films. *J Pharm Sci*, 63 (1), 119-25.

Pasricha, A., Dillard, D. A. & Tuttle, M. E. (1997). Effect of physical aging and variable stress history on the strain response of polymeric composites. *Composite Science and Technology*, 57 (9-10), 1271-1279.

Perera, D. Y. (2002). Effect of thermal and hygroscopic history on physical ageing of organic coatings. *Progress in Organic Coatings*, 44 55-62.

Petereit, H. U., Assmus, M. & Lehmann, K. (1995). Glyceryl monostearate as a glidant in aqueous film-coating formulations. *European Journal of Pharmaceutics and Biopharmaceutics*, 41 (4), 219-228.

Pozharitskaya, O. & Vainshtein, V. (1998). Controlled release of pentoxifylline from polymeric matrices. *Pharmaceutical Chemistry Journal*, 32 (8), 440-442.

Priestley, R. D., Ellison, C. J., Broadbelt, L. J. & Torkelson, J. M. (2005). Structural Relaxation of Polymer Glasses at Surfaces, Interfaces, and In Between. *Science*, 309 (5733), 456-459.

Radtke, G., Knop, K. & Lippold, B. C. (2002). Manufacture of Slow-Release Matrix Granules by Wet Granulation with an Aqueous Dispersion of Quaternary Poly(meth)acrylates in the Fluidized Bed. *Drug Development and Industrial Pharmacy*, 28 (10), 1295-1302.

Schneider, H. (1999). The Meaning of the Glass Temperature of Random Copolymers and Miscible Polymer Blends. *Journal of Thermal Analysis and Calorimetry*, 56 (3), 983-989.

Shah, V. P., Tsong, Y., Sathe, P. & Liu, J.-P. (1998). *In Vitro* Dissolution Profile Comparison - Statistics and Analysis of the Similariry Factor, f_2. *Pharmaceutical Research*, 15 (6), 889-896.

Shao, Z. J., Moralesi, L., Diaz, S. & Muhammadi, N. A. (2002). Drug Release from Kollicoat® SR 30D-Coated Nonpareil Beads: Evaluation of Coating Level, Plasticizer Type, and Curing Condition. *AAPS Pharm. Sci. Tech.*, 3 (2),

Simon, F. (1931). *Z. anorg. allgem. Chem.*, 23 219.

Sinko, C. M., Yee, A. F. & Amidon, G. L. (1990). The Effect of Physical Aging on the Dissolution Rate of Anionic Polyelectrolytes. *Pharmaceutical Research*, V7 (6), 648-653.

Sinko, C. M., Yee, A. F. & Amidon, G. L. (1991). Prediction of Physical Aging in Controlled-Release Coatings: The Application of the Relaxation Coupling Model to Glassy Cellulose Acetate. *Pharmaceutical Research*, V8 (6), 698-705.

Struik, L. C. E. (1978). Chapter 1 - Scope of the Work. In L. C. E. Struik (Ed.) *Physical Aging in Amorphous Polymers and Other Materials* (pp 1). New York: L. C. E. Struik.

Tiemblo, P., Guzman, J., Riande, E., Mijangos, C. & Reinecke, H. (2001). Effect of physical aging on the gas transport properties of PVC and PVC modified with pyridine groups. *Polymer*, 42 (11), 4817-4824.

Vecchio, C., Fabiani, F. & Gazzaniga, A. (1995). Use of Colloidal Silica as a Separating Agent in Film Forming Processes Performed with Aqueous Dispersion of Acrylic Resins. *Drug Development and Industrial Pharmacy*, 21 (15), 1781-1787.

Vesey, C. F., Farrell, T. & Rajabi-Siahboomi, A. R. (2005). Evaluation of plasticizers for Surelease®, an aqueous ethylcellulose dispersion for modified release film-coating. The 32nd Annual Meeting and Exposition of the Controlled Release Society, Miami Beach, FL, 18 June/22 June 2005.

Watano, S., Ando, K., Miyanami, K., Ii, Y. & Sasatani, S. (1997). Preparation of core particles for aqueous film coating using agitation fluidized bed. *Chem Pharm Bull (Tokyo)*, 45 (12), 2039-42.

Wesseling, M. & Bodmeier, R. (2001). Influence of Plasticization Time, Curing Conditions, Storage Time, and Core Properties on the Drug Release from Aquacoat-Coated Pellets. *Pharm. Dev. Tech.*, 6 (3), 325-331.

Wu, C. & McGinity, J. W. (2001). Influence of Ibuprofen as a Solid-State Plasticizer in Eudragit® RS 30 D on the Physicochemical Properties of Coated Beads. *AAPS Pharm. Sci. Tech.*, 2 (4), 1-9.

Wu, C. & McGinity, J. W. (2003). Influence of an Enteric Polymer on Drug Release Rates of Theophylline from Pellets Coated with Eudragit® RS 30 D. *Pharm. Dev. Tech.*, 8 (1), 103-110.

Wu, C. & McGinity, J. W. (2003). Influence of methylparaben as a solid-state plasticizer on the physicochemical properties of Eudragit® RS PO hot-melt extrudates. *European Journal of Pharmaceutics and Biopharmaceutics*, 56 (1), 95-100.

Wu, C. B. & McGinity, J. W. (1999). Non-traditional plasticization of polymeric films. *International Journal of Pharmaceutics*, 177 (1), 15-27.

Wu, C. B. & McGinity, J. W. (2000). Influence of relative humidity on the mechanical and drug release properties of theophylline pellets coated with an acrylic polymer containing methylparaben as a non-traditional plasticizer. *European Journal of Pharmaceutics and Biopharmaceutics*, 50 (2), 277-284.

Yoon, J.-Y., Park, H.-Y., Kim, J.-H. & Kim, W.-S. (1996). Adsorption of BSA on Highly Carboxylated Microspheres – Quantitative Effects of Surface Functional Groups and Interaction Forces. *J. Colloid Interf. Sci.*, 177 (2), 613-620.

Zelko, R., Orban, A. & Suvegh, K. (2006). Tracking of the physical ageing of amorphous pharmaceutical polymeric excipients by positron annihilation spectroscopy. *Journal of Pharmaceutical and Biomedical Analysis*, 40 (2), 249-254.

Zelko, R., Orban, A., Suvegh, K., Riedl, Z. & Racz, I. (2002). Effect of plasticizer on the dynamic surface tension and the free volume of Eudragit systems. *International Journal of Pharmaceutics*, 244 (1-2), 81-86.

Zheng, W. & McGinity, J. W. (2003). Influence of Eudragit® NE 30 D Blended with Eudragit® L 30 D-55 on the Release of Phenylpropanolamine Hydrochloride from Coated Pellets. *Drug Development and Industrial Pharmacy*, 29 (3), 357-366.

Zheng, W., Sauer, D. & McGinity, J. W. (2005). Influence of hydroxyethylcellulose on the drug release properties of theophylline pellets coated with Eudragit® RS 30 D. *European Journal of Pharmaceutics and Biopharmaceutics*, 59 (1), 147-154.

Vita

Shawn Anthony Kucera was born in Bryan, TX on May 28, 1974, the son of John and Therese Kucera. He graduated with Honors from Caldwell High School in May of 1992. While attending Blinn Jr. College in Bryan, TX, Shawn took an interest in firefighting and emergency medical services. He graduated from the Texas Fireman's Training School at Texas A&M and later attended courses at Blinn Jr. College where he received state licensure as a Paramedic. Shawn worked for the College Station Fire Department in College Station, TX from 1995-1998. During this time, he graduated from Blinn College with an Associate's Degree in Fire Science and Technology. Shawn was also inducted into Phi Theta Kappa, the International Honor Society of the Two Year College. In the summer of 1998, Shawn began studies at Texas A&M University in College Station. To support himself during this time, he worked for St. Joseph's EMS, College Station Medical Center, Texas A&M Recreational Sports, Texas A&M Facilities Coordination, and Lynntech, Inc. Shawn graduated with a Bachelor of Arts Degree in Chemistry with a Minor in Psychology in December of 2000 and took a full-time position at Lynntech, Inc. of College Station as a Research Assistant. In August of 2001, Shawn entered the Ph.D. program in Chemistry at The Pennsylvania State University and studied for a short time under the direction of Dr. Ayusman Sen. In August of 2002, Shawn entered the Ph.D. program in Pharmaceutics in the College of Pharmacy at The University of Texas at Austin under the direction of Dr. James W. McGinity. During this time he has served as a teaching assistant and research assistant, attended various scientific conferences where he has presented posters of his research, and also participated in an international industrial internship with Degussa-Röhm Pharma

Polymers in Darmstadt, Germany. Shawn has published research papers in *Drug Development and Industrial Pharmacy* and *Pharmaceutical Development and Technology*. He as also authored a chapter on the physical aging of aqueous lattices in Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, 3rd Ed. Portions of this manuscript have been submitted to *AAPS PharmSciTech* and *The Journal of Drug Delivery Science and Technology*.

Permanent address: 709-A E. 44th St., Austin, TX 78751

This dissertation was typed by the author.